PRACTICAL POINTERS FOR PRIMARY CARE

INDEX

JANUARY – JUNE 2006

MEDICAL SUBJECT HEADINGS

PRACTICAL CLINICAL POINTS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO THE FULL ABSTRACTS

JAMA, NEJM LANCET, BMJ

ARCHIVES INTERNAL MEDICINE,

ANNALS INTERNAL MEDICINE

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This index is a reference document.

It consists of 4 parts:

1) “Medical Subject Headings”: A list of 75 medical subject headings (MeSH) arranged alphabetically. Links are supplied to the “Highlights of Abstracts and *Editorial Comments*” section.

2) “Practical Clinical Points”, a 2-page review. This provides an instant reminder of points of clinical interest and importance which primary care clinicians should considere, be aware of, and advise patients about. Links are also supplied to the “Highlights of Abstracts and *Editorial Comments*” section. .

3) “Highlights of Abstracts and *Editorial Comments*” section. This contains a condensation of each abstract published during the 6-month period. 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* for over 20 years. Links are provided to the detailed full abstract itself through the internet.

4) The abstract itself provides more detailed information and the citation.

This index 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, [1-12] refers to the twelfth article abstracted in January 2006.

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

MEDICAL SUBJECT HEADINGS (MESH) JANUARY- JUNE 2005

PRACTICAL CLINICAL POINTS JANUARY – JUNE 2006

Consider:

- **Including an unobtrusive screen for alcohol use (AUDIT) in the patient-completed history form. [3-3]**
- **Ambulatory BP monitoring under special circumstances. [6-1]**
- **Use of angiotensin-converting-enzyme (ACE) inhibitor in patients with coronary heart disease even if they do not have left ventricular dysfunction. [4-11]**
- **Use of ACE inhibitor in patients with peripheral arterial disease. [5-9]**
- **A trial of glucosamine-chondroitin for patients with osteoarthritis who may wish to try it. [2-9]**
- **Use of inhaled insulin for patients who might be interested. [5-5] [2-3]**
- **Testing and treatment of *H pylori* in patients with long-term troublesome dyspepsia. [1-10]**
- **Permethrin as first-line treatment of scabies. [4-6]**
- **Use of dipyridamole + aspirin for secondary prevention of cerebral ischemia instead of aspirin alone. [5-5]**

Be aware of:

- **The risk (congenital abnormalities) of ACE inhibitors before prescribing for women of child-bearing age. [6-12]**
- **The risk of anti-cholinergic drugs in elders with mild cognitive impairment. [2-6]**
- **The adverse effects (severe exacerbations and death) of long-term use of long-acting beta-agonists in patient with asthma. [6-1]**
- **The risk of atherothrombosis when prescribing traditional NSAIDs as well as COX-2 inhibitors. Consider acetaminophen first. [6-2] [6-3]**
- **The adverse effects of serious illness (eg, mother's breast cancer) on children. [4-10]**
- **The adverse effects and cost of high doses of statin drugs, which are now being advertised to "lower cholesterol as much as possible". [6-4]**
- **That routine colonoscopy screening is less productive as patients become more elderly. There should be an age-related cut-off date. [5-7]**
- **The long-term harms of radiation from CT scans. [5-12]**
- **The spiritual concerns of patients at the end of life. Explore whether they are "at peace". [1-1]**
- **The possible value of fondaparinux (selective factor Xa inhibitor) for patients with venous thromboembolism and myocardial infarction. [2-10] [4-8]**
- **The advisability of discontinuing (or not prescribing) some drugs in old, frail patients. [3-1]**
- **Viruses to be the main cause of pharyngitis. Culture my not be a reasonable choice for diagnosis in primary care. Delayed prescription for penicillin may reduce use of antibiotics. [3-4]**

- **The psychological power of the placebo. A sham device may be more effective than a pill. [2-2]**
- **The benefit / harm-cost of prostate cancer screening. The bloom is coming off. Men should be made aware of risks and benefits before a PSA test is considered. [3-5]**
- **Both biomedical and psychosocial causes of illness at the onset of a new consultation. Somatazation is a joint responsibility of doctor and patient. [2-1]**
- **The expression of care and caring offered by telephone follow-up. [5-2]**
- **Of the availability of the rotavirus vaccine. [1-3]**
- **Of the new tuberculosis blood tests. [1-11]**
- **Of the association between being female and the menses on attacks of migraine. Triptans may be useful in prevention. [4-3]**
- **Of the early signs of meningococcal disease in children and adolescents. Early treatment may be life-saving. [2-11]**
- **Of the pitfalls of screening tests and their proper indications, use, and benefits. [4-7]**
- **Of the difficulties poor patients have in controlling obesity. Be compassionate. [5-10]**

Advise:

- **Patients that caffeine may help keep them awake. [6-11]**
- **Patients of the major adverse effects of trans fatty acids. All patients should avoid them as completely as possible and be aware of the many foods that contain them. [4-1] [4-2]**
- **Women that vitamin D deficiency during pregnancy may be associated with a deficit in bone-mineral accrual in their child. [1-6]**
- **Smokers that tobacco will be responsible for one billion deaths worldwide in the 21st century. [5-3]**
- **Some patients with asymptomatic inguinal hernias that watchful waiting may be an acceptable approach. [1-5]**
- **Patients with gout about benefits of weight loss and diet. [6-9]**
- **Women of childbearing age that physical fitness may reduce risk of gestational diabetes. [3-8]**
- **Patients that weight gain may exacerbate their gastro-esophageal reflux symptoms, and that weight loss may benefit. [6-8]**
- **Women that estrogen-alone does not increase risk of breast cancer. [4-9]**

HIGHLIGHTS AND *EDITORIAL COMMENTS*

JANUARY – JUNE 2006

ADIPOSITY OF THE HEART

Proposing That Fat Accumulations In The Myocardium Are Toxic.

4-12 ADIPOSITY OF THE HEART, REVISITED: A Narrative Review

Under healthy conditions, most triglyceride is stored in adipocytes. The amount of triglyceride stored in non-adipose tissues (pancreas, liver, and myocardium) is minimal and tightly regulated. When this regulation is disrupted, triglycerides may accumulate excessively in these organs (steatosis). The accumulation may culminate in irreversible cell death (lipotoxicity) and lead to several clinical syndromes: non-alcoholic hepatic steatosis; pancreatic B-cell failure; and dilated cardiomyopathy

Investigations are now revisiting the hypothesis that excessive deposits of lipids within myocardial tissue (that is, cardiac lipotoxicity) is an important, but forgotten, cause of non-ischemic dilated cardiomyopathy. Imaging techniques now permit precise and reproducible quantification of intra-cellular triglyceride in various human organs, including the myocardium. This presents a novel mechanism that may act independently of coronary artery disease to cause dilated cardiomyopathy.

"Myocardial lipid content may be a biomarker and a putative therapeutic target for cardiac disease in obese patients."

However. . . "A direct association between myocardial lipid content and left ventricular performance has yet to be reported."

This, of course, is not a practical point at this time. I could not resist abstracting it. Indeed, I am old enough to remember when the concept of the fatty heart was taught in medical school.

This makes sense. If fat can accumulate in the liver, why not in the myocardium?

Watch for further developments.

ALCOHOL

Consider Routine Screening of All Attendees in Primary Care

3-3 OPPORTUNISTIC SCREENING FOR ALCOHOL USE DISORDERS IN PRIMARY CARE

Primary care is the most promising location to offer brief interventions aimed at reducing excessive alcohol consumption. To offer such interventions, clinicians need access to screening instruments with high sensitivity and specificity, which are quick and easy to apply, and are cost effective.

This study evaluated the efficacy of different screening methods for identification of alcohol abuse, including the Alcohol Use Disorders Identification Test **(AUDIT)**.

In six general practices, 194 male patients responded to the AUDIT questionnaire which was embedded within a general lifestyle questionnaire.

Alcohol dependence was determined using the DSM IV.

For comparison, measured 4 biochemical blood levels which have been indicators of alcohol abuse: gamma-glutamyltransferase; aspartate aminotransferrase; percent carbohydrate deficient transferrin; and erythrocyte mean cell volume.

AUDIT was much more highly correlated with alcohol problems; hazardous consumption; monthly binge drinking; weekly binge drinking; and alcohol dependence than any of the biochemical markers. AUDIT had areas under the curve of 0.94 to 0.96 for all classifications of alcohol use disorder.

For identification of hazardous alcohol consumption, AUDIT score of > 8 had moderate sensitivity (69% [69% true positives *vs* 31% false negatives]; and high specificity (98% [98% true negatives *vs* 2% false positives].)

If the test was positive, it predicted an alcohol problem 97% of the times; if the test was negative, it predicted no alcohol problem 75% of the times.[1] This was much more indicative of problems than the biochemical markers.

"A positive questionnaire score is a good indication of hazardous alcohol consumption, and a negative score is a good indication of no alcohol dependence."

The study embedded the AUDIT questionnaire in a longer health-related instrument which primary care patients completed. As such, it appears to be less intrusive.

Practical Pointers has abstracted a number of articles addressing alcohol-screening tests over the years. And has reported that identification of problem drinkers and confronting them with the possible problem is effective in reducing consumption. If screening were not somewhat effective, there would be no reason to screen.

1 *The predictive values of positive tests = true positive tests (69%) divided by sum of true positive tests (69%) plus false positive tests (2%) = 69/71 = 97.*

The predictive value of negative tests = true negative tests (98%) divided by the sum of true negative tests (98%) plus false negative tests (31%) = 98/129 = 75

Go to GOOGLE "Alcohol Use Disorders Identification Test" to download a copy.

Do Wine Drinkers Have A More Healthy Diet?

3-6 FOOD BUYING HABITS OF PEOPLE WHO BUY WINE OR BEER

This study investigated whether people who drink wine buy healthier foods than people who drink beer.

Obtained data from 3.5 million transactions in Danish supermarkets; 5.8% of customers bought wine but no beer; 6.6% bought beer, but no wine; 1.2% bought both.

Compared 40 categories of food bought by wine purchasers *vs* beer purchasers.

Wine buyers bought more olives, fruit, vegetables, poultry, cooking oil, and low fat cheese.

Beer buyers bought more ready cooked dishes, sugar, cold cuts, chips, pork, butter, margarine, sausages, lamb, and (especially) soft drinks.

Wine buyers were more likely to buy "Mediterranean" diet food items; beer buyers more likely to buy "traditional" food items.

Wine tends to be drunk with meals, in modest amounts. This may have metabolic advantages.

The reported influence of type of alcoholic drink on mortality could be due to insufficient adjustment for lifestyle factors.

The "French paradox" indicates that the high consumption of wine in France (and its protective effect) more than overcomes the harmful effects of fatty foods (which the French people presumably eat in high quantities).

Epidemiological studies indicate a strong protective effect of modest daily alcohol consumption on risk of coronary heart disease. Whether wine (specifically red wine) is responsible has been debated. Some studies report that the type of alcohol is not relevant.

Epidemiological studies contain many confounders. In regard to the protective effect of wine, the accompanying type of diet must be a major confounder.

A recent meta-analysis (comment on by BMJ April 8, 2006; 332: 811) suggests that the epidemiological findings of the putative protective effect of alcohol maybe in error because the control groups (abstainers) were misclassified. Many "abstainers" were really persons who had stopped drinking because of ageing or ill health. This resulted in an increase in death among "abstainers" which was misinterpreted to be due to a lowering of death in the drinkers.

Modest intake of wine is an essential component of the healthy Mediterranean diet.

Moderate Alcohol Consumption Reduces Risk of CHD in Middle-Age

5-6 PROSPECTIVE STUDY OF ALCOHOL DRINKING PATTERNS AND CORONARY HEART DISEASE IN WOMEN AND MEN

Prospective epidemiological studies have reported a lower risk of coronary heart disease **(CHD)** among consumers of *moderate* amounts of alcohol as compared with abstainers. Results consistently imply that the pattern of drinking is important, and that steady (eg, daily; several times a week) drinking is beneficial.

This study determined the association between drinking patterns and CHD among middle-aged men and women.

The amount of alcohol intake was inversely associated with CHD among *both* men and women. Adjusted hazard ratio of CHD *decreased* progressively in a graded manner as number of drinks per week *increased* from 0 to 7, to 14, and to >28 in women and to > 35 in men.

Among men, drinking frequency (days per week), not amount of alcohol intake, seems more important in reducing risk of CHD. Among women, alcohol intake (total amount per week) may be the primary determinant of the inverse association.

It may be that heavy drinkers and abusers of alcohol have less risk of CHD than abstainers and moderate drinkers. The risks of heavy drinking far outweigh any benefit.

Some commentators recently have doubted the association between frequent and moderate alcohol consumption and reduction in risk of CHD. I believe the important message of this study is a confirmation of previous studies reporting benefit of reducing risk of CHD (for both men and women) who drink frequently but

moderately. Women (and men) who binge drink are obviously at great risk of adverse effects of alcohol. Whether this reduces risk of CHD is irrelevant.

I do not believe the observation that amount of drinking in women confers less risk of CHD is clinically important. Frequency of moderate drinking in women (as in men) is associated with lower risk of CHD, and may be clinically important. I believe the same advice pertains to women and men (and physicians as role models): If you wish to drink, and enjoy drinking, have one drink before dinner, or one glass of wine with dinner.

AMBULATORY BLOOD PRESSURE MONITORING

Better Estimate of Risk in the Individual

6-1 AMBULATORY BLOOD PRESSURE MONITORING

Our knowledge about risks of hypertension and the benefits of treatment is based on taking a small number of readings with the traditional auscultatory technique in a medical setting. Such measurements have been of enormous value on a population basis, but often provide a poor estimate of risk of an individual. This may be due in part because of poor technique of the observer, the "white coat" effect, and the inherent variability of blood pressure **(BP**).

Any clinical measurement of BP may be regarded as a surrogate measure for the "true" BP of the patient, defined as the mean level over prolonged periods.

Two techniques have been developed to improve the estimate of the "true" BP: 1) ambulatory BP monitoring (**ABPM**), and 2) home BP monitoring. Home monitoring may be used to supplant ABPM, but it is not included in most studies documenting the superiority of ABPM over traditional BP measurements.

This review considers ABPM only.

ABPM can provide: 1) the mean 24-h BP, 2) diurnal rhythm of BP, and 3) BP variability.

ABPM in other clinical conditions:

White coat hypertension

Labile BP

Resistant hypertension

Masked hypertension

Postural hypotension

Evaluating response to drugs

Predictions of clinical outcomes.

This is a concise, informative, and readable review. You may wish to read the full abstract and the original.

In my experience as a patient, determination of BP in doctor's offices is often done improperly. There may be little opportunity to relax before the BP is taken. Usually, only one determination is made, and the observer then states "Your blood pressure is X/Y " Accurate BP determinations are essential for the well being of all.

I believe many patients with "high blood pressure" receive drug therapy unnecessarily—mainly those with WCH. Home measurements will allow many patients to discontinue drugs.

Lifestyle interventions are essential in patients with WCH

I believe all patients with elevated BP should be monitored at home. Accurate automated machines are available of $100 or less. They provide easily repeated and reasonably accurate observations. Patients may fully relax and take several readings to obtain an average. They will help diagnosis of WCH. They will monitor response to therapy. In general practice, repeated home BP measurements are more revealing and practical than ABPM. Home BP may reduce number of doctor visits and pay for the machine.

If a machine is available at home, persons who do not have hypertension may check their BP once or twice a year. I would advise patients to avoid BP machines such as those available in pharmacies where readings may be similar to clinic readings.

ABPM should be reserved for special circumstances.

Monitors cost about $3000.

ANGIOTENSIN CONVERTING ENZYME INHIBITORS

4-11 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH CORONARY HEART DISEASE AND ABSENCE OF HEART FAILURE OR LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

"Angiotensin-converting enzyme inhibitors (**ACE**) . . . **"**are an undisputed treatment in patients who have congestive heart failure **(HF),** or in patients with coronary heart disease **(CHD)** and concomitant left ventricular dysfunction."

This meta-analysis assessed long-term effects of ACE in patients who have CAD and no signs of HF or severe left ventricular dysfunction. (Stable coronary artery disease.)

Treatment ACE inhibitors included ramipril, quinapril, enalapril, perindopril, and trandolapril.

Overall results:	Active treatment	Placebo	Absolute difference	NNT (4-y)
	n = 16 328 (%)	n = 16 034 (%)	(% in 4.4 years)	
All-cause death	1215 (7.4)	1392 (8.7)	1.3	77
CV death	673 (4.1)	819 (5.1)	1.0	100
MI	1048 (6.4)	1258 (7.8)	1.4	71
Stroke	342 (2.0)	445 (2.7)	0.7	142

Use of ACE inhibitors for long-term secondary prevention in patients with established CHD, who are without LV dysfunction or heart failure, was associated with a reduction in all-cause mortality and major cardiovascular events.

Note that elevated BMI, smoking, hypertension, and dyslipidemia were present in many patients at baseline. The study did not consider influence of these factors on outcomes. Apparently, many of these factors were not treated or were under treated. The study concentrated on taking a pill or not taking a pill.

I believe correcting these risk factors would improve prognosis much more than taking a pill once a day.

What about cost? My pharmacy quotes $2.23 for one 10-mg ramipril (Altace). This would cost the patient about $3260.00 over four years. You may ask. . . "Would you pay over $3000.00 for a one in 100 chance of

avoiding death from a cardiovascular cause over 4 years? And at the same time incurring considerable adverse effects from the drug?

Clinically Significant Increase In Walking Distance

5-9 RAMIPRIL (An ACE Inhibitor) MARKEDLY IMPROVES WALKING ABILITY IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

Randomized, double-blind placebo-controlled trial followed 40 patients (mean age 66; almost all male) with symptomatic peripheral artery disease (**PAD**). None had a history of diabetes or hypertension.

Forty two % were smokers. Many had hypertension. In some, LDL-cholesterol levels exceeded 100 mg/dL. Only 27% were on lipid-lowering therapy.

Asked participants to refrain from exercise, smoking, and caffeine for 24 hours before testing.

Randomized to: 1) ramipril 10 mg daily, or 2) placebo for 24 weeks.

Measured pain-free and maximum walking time during a standard treadmill test.

Completed a Walking Impairment Questionnaire. (**WIQ**)

Treadmill test

At baseline:	Placebo	Ramipril
Median pain-free walking time (s)	168	160
Maximum walking time (s)	244	234
At 24 weeks		
Median pain-free walking time (s)		387
Maximum walking time (s)	234	685

The WIQ in the ramipril group indicated improvement in scores of walking distance, speed, and stair climbing. The increase in walking distance (calculated as a mean of 400 meters in the ramipril group) is clinically significant and would appreciably affect daily functional capacity. The improvements in the WIQ scores were consistent with the measured improvements, demonstrating that ACE improves the ability to perform daily activities.

I do not know why the trial excluded patients with diabetes and hypertension.

Note that the trial was drug vs no-drug. It did not address risk factors which primary care clinicians would treat in addition to drug therapy. Smoking cessation was not stressed. (Subjects were asked to stop smoking for 24 hours before testing). Dyslipidemia was not aggressively treated. Outcomes may have differed if these risks had been treated, and ACE therapy may not have resulted in as great an improvement.

I would be willing to add an ACE as a therapeutic trial in these patients.

Angiotensin II Blockers as Well

6-12 ACE INHIBITORS AND CONGENITAL ABNORMALITIES

When ACE inhibitors (**ACE**; eg, *Captopril*; the prototype) are used in the second half of pregnancy, they can cause major congenital abnormalities. These effects result from blockade of conversion of angiotensin I to

angiotensin II in the developing fetal kidneys. A similar pattern has been reported after treatment with angiotensin II- receptor-antagonists.

A study in this issue of NEJM reports that major congenital abnormalities may also occur if ACE are taken during the *first* trimester of pregnancy.

All drugs are foreign to the body. All drugs should be avoided in pregnancy. This essentially means that all women of child-bearing age should avoid drugs unless they are considered essential, or it is established without a doubt that they will not become pregnant. No tobacco; no alcohol; no drugs.

Almost half of all pregnancies are unintended.

Primary care clinicians must be among the major prescribers of ACE. Acting on this information may prevent a major catastrophe.

ANTICHOLINERGIC DRUGS

Associated With Significant Deficits in Cognitive Functioning

2-6 NON-DEGENERATIVE MILD COGNITIVE IMPAIRMENT IN ELDERLY PEOPLE AND USE OF ANTICHOLINERGIC DRUGS

Dysfunction of the cholinergic system has a detrimental effect on cognitive performance. The anticholinergic agent, scopolamine, reduces hyppocampal activation, and, when given to young adults, produces cognitive defects characteristic of aging-related changes, rather than dementia.

Drug consumption in elderly people is high. Many commonly prescribed drugs have anticholinergic effects (antiemetics, antispasmodics, bronchodilators, antiarrhythmic drugs, antihistamines, analgesics, antihypertensives, antiparkinsonian agents, corticosteroids, skeletal muscle relaxants, ulcer drugs, and psychotropic drugs). These are likely to have a more toxic effect in an aging brain because of increased permeability of the blood-brain barrier, slower metabolism and drug elimination, and polypharmacy.

Doctors commonly fail to associate cognitive dysfunction in elderly people with anticholinergic agents. They also underestimate anticholinergic toxicity, and prescribe such drugs at high doses. An increasing number of such compounds are available without prescription.

This study tested whether drug-induced anticholinergic burden is associated with cognitive dysfunction.

Of the 372 subjects, 51 (14%) were taking at least one anticholinergic drug at baseline. None were taking acetylcholinesterase inhibitors. At the end of the year, 30 of 51 were still taking the drugs regularly.

Compared with the 297 non-users, the 30 continuing users had poorer performance on reaction time, attention, memory, visuospatial construction, and language tasks. 80% were classified as having mild cognitive impairment, compared with 35% of non-users.

This is an important contribution. I was not aware that so many drugs have anticholinergic activity. I believe also that few primary care clinicians are aware of them.

Before assuming that your patient has early dementia from Alzheimer's disease and prescribing a acetylcholinesterase inhibitor, consider if any drug you are prescribing could be related to beginning "dementia".

The message applies to many other drugs used in geriatric practice. Many carry unsuspected and undetected adverse effects in some individuals. Primary care clinicians should be constantly aware that adverse drug effects may occur more frequently in the elderly, and may present in diverse ways. Continually ask—could any drug I prescribed adversely affect this patient? Or is any non-prescription drug?

I hope a follow-up study will measure effects of discontinuing these drugs.

ARTHRITIS

Combined G and C May Be Effective In the Subgroup with Moderate-To-Severe Pain.

2-9 GLUCOSAMINE, CHONDROITIN SULFATE, AND THE TWO IN COMBINATION FOR PAINFUL KNEE ARTHRITIS

This randomized, double-blind, placebo-controlled trial compared glucosamine sulfate (G), chondroitin (C), both, celecoxib, and placebo for 6 months in over 1500 patients with knee osteoarthritis.

Product selection: The study was conducted under an investigational new drug application. As such, C and G were subject to pharmaceutical regulation by the FDA. Ingredients were tested for purity, potency and quality. [1]

Primary outcome = a 20% decrease in pain from baseline to 24 weeks based on a pain score.

Overall, for all randomized patients, C and G were *not* significantly better than placebo in reducing knee pain by 20%. Change in WOMAC pain score for placebo = -86 points; for G + C = -100 points.

The rate of response to placebo was high (60% reported a decrease in pain of 20% or more). As compared with placebo, the rate of response to G was 4% higher. And the rate of response to C was 5% higher. The rate of response to both C and G combined was 10% higher. (Not statistically significant.)

Overall, response to celecoxib was 10% higher than to placebo. And response time was much faster than for C and G.

For patients with moderate-to-severe pain, the rate of response to C + G combined was significantly higher than for placebo (79% vs 54%). Change in *mean* WOMAC pain scores from baseline to end of follow=-up = -123 points in the placebo group vs -153 points in the C + G group. (Statistically significant.)

For patients with moderate-to-severe pain, G +C was associated with a *greater* reduction in pain than celecoxib: - 177 points vs - 153 points.

A 20% reduction in pain seems a very modest goal.

1 *This is unusual. Most studies of "dietary supplements" do not screen products so carefully. This study was detailed, carefully crafted, executed, and analyzed from a statistical standpoint.*

2 *Does lack of "statistical" significance preclude a prescription? I believe not. There will always be patients whose response to treatment deviates from the mean, either less favorably or more favorably. Response to C + G must be evaluated in an individual patient.*

Would I prescribe C + G for a patient with OA pain? I would prescribe acetaminophen first. In view of the safety of C +G, I would mention the combination as a possibility for the patient to consider—at least to try.

I would suggest they purchase the preparation at a national-chain pharmacy rather than by mail or on the internet. I believe it would be more likely to be as labeled.

Although primary care clinicians may not admit it, I believe many do indeed rely on the placebo effect, at least accept it when a patient reports improvement.

At my pharmacy, G (1500 mg)+ c (1200 mg) costs $32 for 120 tablets. At times, it is on sale at about half price. Celebrex 200 mg costs $ 3.19 each

ASPIRIN

Prevents Stroke In Women; MI In Men

1-7 ASPIRIN FOR THE PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN WOMEN AND MEN *A Sex-Specific Meta-Analysis Of Randomized Controlled Trials*

The American Heart Association has reported aspirin therapy is effective in *primary* prevention of coronary heart disease in adults of both sexes who are at increased risk. The AHA guidelines on primary prevention recommend low-dose aspirin in women whose 10-year risk of a first coronary event exceeds 20%, and consideration for those with a 10-year risk of 10% to 20%.

This meta-analysis determined if benefits and risks of aspirin therapy in primary prevention differed between men and women.

In absolute terms:

A. Women: Aspirin for an average of 6 years resulted in a benefit of approximately 3 cardiovascular events and 2 strokes prevented per 1000 women. No effect on MI or cardiovascular mortality.

B. Men: Aspirin for an average of 6 years resulted in a benefit of approximately 4 cardiovascular events prevented per 1000 men. MI was significantly reduced (absolute benefit of 1 MI per 125 men treated). No statistically significant reduction in stroke.

Major bleeding (mainly GI) occurred over 6 years in 1 of every 400 women and 1 in 300 men.

(2.5 major bleeds per 1000 women and 3 per 1000 men.)

The benefits of aspirin for primary prevention do not approach the substantial benefits in secondary prevention.

When negotiating a treatment plan with women who may be interested in aspirin for primary prevention of CVD, clinicians may tell them the benefit over 6 years in preventing ischemic stroke is 1 in 500. The risk of major bleeding is 1 in 400 .

Men may be told the benefit over 6 years in preventing MI is 1 in 150. And the risk of major bleeding is 1 in 300.

Note that these benefit and harm effects in this study occurred in persons considered healthy.

Do the benefits outweigh the harms? In this study, benefits and harms balanced about equally.

Individuals may decide for themselves after being fully informed. It depends on an estimation of the risk of CVD in each individual. In individuals at higher risk, aspirin for primary prevention may be associated with greater benefit.

Caution when prescribing primary prevention aspirin in patients with hypertension. Hypertension is the major risk for hemorrhagic stroke. Aspirin may be more dangerous in patients with hypertension because of its association with hemorrhagic stroke. BP should be well-controlled before aspirin is prescribed for primary prevention.

Should We Treat With Drugs Alone, and Ignore Other Risk Factors?

5-8 ASPIRIN PLUS DIPYRIDAMOLE VERSUS ASPIRIN ALONE AFTER CEREBRAL ISCHEAMIA OF ARTERIAL ORIGIN

This remarkable multicountry, secondary prevention trial randomized over 2700 patients for 3.5 years to aspirin alone (median 75 mg daily), or aspirin + dipyridamole (200 mg twice daily, mainly as extended release). All had experienced a TIA or a non-disabling (*minor)* ischemic stroke.

At randomization, 18% had diabetes; 60% had hypertension; 47% had hyperlipidemia; and 36% smoked.[1]

More patients on the combination discontinued trial medication (470 vs 184) mainly due to headache, a common adverse effect of dipyridamole.

Primary outcome = a composite of non-fatal stroke, non-fatal myocardial infarction, or death from vascular causes.

Results (3.5-y)	Combined A + D (n = 1316)	Aspirin alone (n = 1376)	Absolute diff	NNT 3 y
Primary outcome	13%	16%	3%	33

The authors conclude: "Our findings show that the combination of aspirin and dipyridamole is more effective than aspirin alone in the prevention of new serious vascular events in patients after non-disabling cerebral ischaemia of presumed arterial origin."

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1 *There was no mention about efforts to treat these major risk factors. I presume the investigators intervened at least in some patients. Trials such as this, which randomize subjects to drug vs drug, or drug vs no-drug,, consider only the effect of the drug. This is not the way primary care works. In the real world of practice, every effort is made (or should be made) to reduce all risk factors in addition to prescribing a presumably helpful drug. I believe there would have been a considerable difference in outcomes in this study (with less benefit from the combined group vs aspirin alone) if all risk factors were treated. And, a much larger cohort of subjects would have been needed to determine any difference in outcome.*

Should primary care clinicians advise the combination to this subset of patients? I believe that many primary care patients would not adhere to the regimen for 3 years. A large number would withdraw.(Primary care patients are much less adherent than subjects in studies.) In addition, others would withdraw because of headache and bleeding. Informing patients that, over 3 years, there is only one chance in 33 of benefit at a cost of over $2300 would discourage some.

ASTHMA

L-ABAs Increase Severe Life-Threatening Asthma Exacerbations and Deaths.

6-10 EFFECT OF LONG-ACTING BETA-AGONISTS ON SEVERE ASTHMA EXACERBATIONS AND DEATH: *Meta-analysis*

Regular use of L-ABAs is associated with an adaptive response, with tolerance to the drug's effects, and a worsening of disease control.

This meta-analysis included 19 placebo-controlled trials (over 33 000 patients) that lasted at least 3 months. which included long-term use of two L-ABAs: salmeterol (*Advair; Serevent*) and formoterol (*Foradil*).

All trials permitted use of as-needed short acting beta-agonists, including the placebo groups. The trials therefore compared L-ABAs + short acting beta-agonists *vs* placebo + short-acting beta-agonists. Many patients were also receiving long-term inhaled corticosteroids.

Odds ratios L-ABAs vs placebo:

Severe exacerbations	2.6
Life-threatening exacerbations	1.8
Deaths	3.5

Difference in absolute terms (*My calculations from figure 2 and figure 3 page 908. RTJ*)

Hospitalizations	110/10 000 / year
Life threatening	15/10 000 / year

Asthma-related deaths: about 1 per 1000 person-years of life

Salmeterol is one of the most frequently prescribed medications in the world--an estimated 3.5 million users in the US. "This indicates that salmeterol may be responsible for about 4000 of the 5000 asthma-related deaths that occur in the United States each year."

Use of L-ABAs is widespread and frequent. Certainly, they give relief to many patients with asthma. I believe the message is not to discontinue regular use, but to monitor use more carefully.

ATHEROTHROMBOSIS

All, Except Possibly Naproxen, Carry Some Risk of Atherothrombosis.

6-2 DO SELECTIVE CYCLO-OXYGENASE-2 INHIBITORS AND TRADITIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INCREASE THE RISK OF ATHEROTHROMBOSIS?

A Meta-analysis of Randomised Trials

. This meta-analysis included 138 randomized trials comparing selective COX-2 inhibitors versus 1) placebo, and 2) traditional non-selective NSAIDs. All studies included information about serious vascular complications (myocardial infarction [**MI**], stroke, and vascular death).

Selective COX-2 inhibitors vs placebo:

An increased risk associated with the former (1.2% per year vs 0.9% per year) [Absolute difference = 0.3%; NNT to harm one patient over 1 year = 333.]. This was chiefly attributed to an increase in risk of MI (0.6 per year vs 0.3 per year) with little apparent difference in other vascular outcomes.

"There was no significant heterogeneity among the different selective COX-2 inhibitors."

Traditional NSAIDs versus placebo:

	Rate ratio for vascular events
Naproxen vs placebo	0.92 (Ie, less risk than placebo)
Ibuprofen vs placebo	1.5
Diclofenac vs placebo	1.6

Selective COX-2 inhibitors vs traditional NSAIDs:

Overall, there was no significant difference in incidence of serious vascular events between 1) selective COX-2 inhibitors and 2) traditional NSAIDs—340 vascular events during over 33 000 person years of exposure to 1), and 211 vascular events in over 22 000 person-years of exposure to 2). [1% per person-years vs 0.9% per person-years.

Selective COX-2 inhibitors were associated with a 1.4-fold increased risk of serious vascular events largely due to a two-fold increase in myocardial infarction.

High doses of ibuprofen and diclofenac were associated with a similar increased risk.

High doses of naproxen were *not* associated with increased risk.

Traditional NSAIDs also inhibit the enzyme COX-2. If selective COX-2 inhibitors are associated with increased risk, it would seem reasonable to assume that traditional NSAIDs would also increase risk.

Do patients with higher baseline risks of MI have higher risk of MI associated with COX-2 inhibitors? If so, would not reduction of other risk factors (smoking, dyslipidemia, hypertension) reduce the risk of MI associated with COX-2 inhibitors and higher-risk traditional NSAIDs? Would it be more dangerous to prescribe NSAIDS to these patients?

All NSAIDs except naproxen (Generic; Naprosin) carry risk of atherothrombotic disease, especially when used for long periods at high doses. We should not forget that NSAIDs have adverse effects on the kidney, blood pressure and heart (increasing risk of congestive failure).

I believe the widespread acceptance and use of COX-2 inhibitors is a tribute to the marketing skills of drug companies.

ATRIAL FIBRILLATION

Once Burned; Twice Shy

1-2 IMPACT OF ADVERSE EVENTS ON PRESCRIBING WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

This study quantified the influence of physicians' experiences of adverse events in patients for whom they had prescribed warfarin on their subsequent prescribing practices.

Considered patients who experienced severe gastrointestinal bleeding or hemorrhagic stroke while taking warfarin during the 120 days before admission to the hospital. Determined likelihood that the doctor who prescribed the warfarin would prescribe it to the next patient presenting with AF. (If a physician treated a patient

with warfarin and the patient had serious bleeding, would this experience influence prescribing warfarin for a second patient who has AF?)

Also considered patients with AF who experienced an ischemic stroke during the preceding 120 days for whom the doctor had *not* prescribed warfarin. Determined the likelihood that the doctor would prescribe warfarin to the next patient with AF who consults him.

Over 500 physicians treated a patient with AF who had major bleeding while on warfarin, and then treated another patient with AF within the next 90 days.

The odds that a physician would prescribe warfarin for a second patient were 21% lower after a first patient experienced bleeding. (Some physicians were reluctant to again prescribe warfarin.)

Conversely, there were no significant changes in warfarin prescribing after a patient had a stroke while *not* taking warfarin. (Physicians were *no more likely* to prescribe warfarin for a second patient with AF despite this adverse outcome.)

“Doctors are neither passive recipients of, nor simple conduits of, clinical evidence.” We conduct an “inner consultation” with evidence, analyzing it in both a logical and intuitive way. In doing so, we are more likely to recall events which are more easily recalled. And the “chagrin factor” tends to make doctors avoid actions that cause them hassle.

Patients conduct similar internal consultations, adding the experience of a consultation to their previous intellectual and emotional understanding of illness.

“Statistical experience” and “clinical experience” guide consultations. These are not enough to clarify the dynamic interaction between patient and doctor. A third dimension is “personal significance”, a concept that captures the reciprocity of the evaluation and interpretation of a new idea by a doctor and patient together. At stake here is something quite profound, and poorly accepted within the medical community—the personal participation of the knower in all acts of understanding. Comprehension is neither an arbitrary nor passive act. It requires tacit skills of judgment.

“In medical consultations there are two participants, both personally knowing, both passionately participating, but from different perspectives, different “somewheres”. The outcome of their interaction in the form of clinical decision is an emergent property of two ways of knowing: biomedical and biographical.

The study illuminates this murky area and provides convincing evidence that within each doctor, these two ways of knowing compete for influence.

Patient’s prior experience plays a major role in acceptance and compliance with therapy. This study points out that doctors respond to prior experience as well.

Patients and doctors consider adverse events due to commission more seriously than adverse events due to omission. When a patient with AF bleeds while he is taking warfarin, warfarin and the doctor who prescribes it get the blame (whether at fault or not). When the patient experiences an ischemic strike, there is doubt about whether warfarin would have prevented it. (It may not have prevented it.) Warfarin and the doctor would less likely be blamed.

Prior experiences and “personal knowledge” do indeed influence subsequent practice.

Do not patients' "personal beliefs" have a much greater influence on their acceptance and compliance with treatments? Eg, belief in a placebo; belief in many "alternative medications"; belief in the advertisements of drug companies; beliefs based on ethnicity and family lore, belief in anecdotal experiences and advice of family and friends; belief in health advice given in the press, on TV, and in the Internet.

Do not physicians' "personal beliefs" influence the treatments they advise to a greater extent than evidence-based therapy? Eg, belief in the latest advertised drug; belief in the suggestions of colleagues given in curbside consultations; belief based on their educational experiences and past training which have become outdated; belief in anecdotal evidence from small, unsubstantiated observational studies, and even "alternative medicine".

BODY MASS INDEX

Obesity Per Se In Middle Age Is A Risk Factor For CVD And Diabetes In Older Age

1-4 MIDLIFE BODY MASS INDEX AND HOSPITALIZATION AND MORTALITY IN OLDER AGE

Does excess weight in middle life confer higher risk of cardiovascular disease (**CVD**) and diabetes in older age? Does a high body mass index (**BMI**) *per se* confer risks over time independent of its effect on BP and lipids?

This prospective study, begun in 1967-73, entered over 17 000 subjects age 31 to 64 (mean age = 45). All were free of coronary heart disease **(CHD)** , diabetes, and major electrocardiography abnormalities.

At baseline, classified CVD risk as: 1) Low risk: BP < 120/80; total cholesterol < 200; and non smoking. 2) Moderate risk: BP 121-139/81-89; total cholesterol 200-239; non smoking; 3) Higher risk groups included subjects with any 1, 2, or 3 risk factors (BP > 140/90; total cholesterol > 240; and current smoking.

BMI categories: normal 18.5-24.9; overweight 25-29.9; obese 30 and over.

At baseline, only 7% of the entire cohort over 17 000 were at low risk. And only 4% were at both low risk and normal BMI.

Low risk group: (normal BP, normal cholesterol, and non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes
Normal BMI	30	40	44
Overweight	42	49	110
Obese	44	112	265

Moderate risk group: (moderately elevated BP and cholesterol, non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes
Normal BMI	42	53	60
Overweight	49	95	122
Obese	89	104	240

In higher risk groups (including smokers) as BMIs rose, outcomes rose in a similarly graded fashion. Within each risk stratum, the risk was higher for overweight and obese persons than for normal weight persons.

Non-smoking individuals with normal BP and normal total cholesterol who are obese in middle age have a higher risk of hospitalization and mortality from CHD and diabetes in older age than those whose weight is

normal in middle age. This risk relationship extends to those with higher cholesterol and BP and to those who smoke.

If You Can't Lose Weight, at Least Get in Better Physical Shape.

3-2 ASSOCIATION OF PHYSICAL ACTIVITY AND BODY MASS INDEX WITH NOVEL AND TRADITIONAL CARDIOVASCULAR BIOMARKERS IN WOMEN

More than half the US population does not meet recommended levels of physical activity, and 65% are overweight. The problem is more common in women than in men.

This study asks: Are a high BMI and low physical activity associated with adverse biomarkers for cardiovascular disease? Which of the two is most strongly associated?

Women's Health Study entered over 27 000 apparently healthy women (mean age 55 at baseline) in 1992-95. Mean BMI = 26. Median leisure physical activity = 601 kcal/wk.

Main outcome measure = association of BMI and physical activity with levels of C-reactive protein, HDL-cholesterol, LDL-cholesterol, total cholesterol, fibrinogen, and apolipoprotein A1.

Higher levels of BMI and lower levels of physical activity were independently associated with adverse levels of almost all lipid and inflammatory biomarkers.

There were stronger associations with BMI than with physical activity. Adipose tissue, particularly visceral adipose tissue, is metabolically active, promoting a thrombotic and inflammatory state as well as a atherogenic lipoprotein state.

Within each BMI category being physically active was associated with more favorable cardiovascular biomarker levels. A modest level of physical activity (about 2.5 hours weekly) was significantly associated with more favorable biomarkers, even in overweight and obese individuals.

The main message for primary care might be—If you can't lose weight, at least get in better shape physically. It would be better, however, if you lose weight and get in better shape.

It is very unlikely that an overweight or obese person will lose weight and maintain the loss with diet alone. A combination of calorie restriction and increased physical activity is required.

BREAST CANCER

No Increase In Risk of BC. An Increase in Need for Repeat Mammography

4-9 EFFECTS OF CONJUGATED EQUINE ESTROGENS ON BREAST CANCER AND MAMMOGRAPHY SCREENING IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

Epidemiologic studies have suggested an increased risk of breast cancer **(BC)** in women receiving estrogen.

This trial compared incidence of BC in hysterectomized women who received estrogen-alone vs placebo

The Women's Health Initiative **(WHI)** enrolled over 10 500 postmenopausal women (age range 50-79; majority over age 60). All had a prior hysterectomy. Randomized to: 1) 0.625 mg combined equine estrogen (**CEE**; *Premarin*) or 2) placebo. Follow-up = 7 years.

After a mean of 7-years, the hazard ratio of invasive BC in women receiving estrogen-alone was 0.80

compared with those receiving placebo. [95% confidence interval = 0.62 to 1.04—not quite statistically significant.]

	CEE (n = 5310)	Placebo (n = 5429)	Absolute difference
Invasive BC	104 (2.0%)	133 (2.5%)	0.5%
Ductal carcinoma	61 (1.1%)	88 (1.6%)	0.5%

The number of women recalled for repeat mammography was higher in the CEE group. At one year, 9% had mammograms with abnormalities which required follow-up vs 5.5% in the placebo group. Absolute difference = 4.5%. (NNT = 22) This pattern continued throughout 7 years (36% vs 28%) Absolute difference = 8%. (NNT = 15)

In this trial, incidence of invasive BC did not differ significantly (statistically) between women receiving CEE vs placebo over 7 years. "This outcome was surprising considering prior evidence that CEE increased risk of BC."

The major consideration–estrogen-alone does not increase risk of BC.

The evolution of hormone replacement therapy for menopausal symptoms is fascinating.

I believe that primary care clinicians can now inform symptomatic post-menopausal women:

A. Combined E + P does slightly increase risk of CHD, stroke, BC, and thromboembolism. Women at risk may wish to avoid E+P treatment (although there is no good alternative to estrogen). Alternatively, women at increased risk may wish to accept preventive therapy to reduce risk. And to take low doses for limited duration.

B. Estrogen-alone does not increase risk of BC. It may slightly increase risk of stroke and thromboembolism. Again, they may wish to accept preventive therapy to reduce risks, and take low doses of estrogen for limited periods.

You Really Can't Keep It A Secret—Don't Try.

4-10 BREAST CANCER IN THE FAMILY—CHILDREN'S PERCEPTIONS OF THEIR MOTHER'S CANCER AND ITS INITIAL TREATMENT

This study explored the accounts of mothers with breast cancer **(BC),** and their children (age 6 to 18) , to identify children's awareness and understanding of their parent's cancer; their reactions to the diagnosis; and what information they would have liked to have been given and seemed to need. And to contrast children's accounts with the mother's perceptions of their children's knowledge.

All children (except two of the youngest) said they had heard of cancer before their mother's illness

Some mothers thought their children did not know that cancer could be life-threatening, and were shocked when the children's comments or questions revealed concerns that she might die.

Children often suspect there is something wrong before they are told—from changes in the mother's mood and overheard conversations.

The reactions of younger and older children were remarkably similar. They described emotional upset, shock, tears, fear and anxiety. Some expressed anger at God, and at the mother herself. Some mothers found it hard to cope with an apparently selfish reaction.

Some children saw surgery and anesthesia as potentially fatal.

Some children considered chemotherapy, with its debilitating side effects and hair loss, was the worst aspect of treatment. Hair loss was a key issue for children across the age range.

Only children under 10 years said that they had been given enough information. Girls wondered whether they might be more likely to develop breast cancer.

Parents may underestimate their children's need for information and try to protect them. "However, the more the children are prepared and informed, as appropriate for their age and development, the more it seems to help them cope.

"Although children cannot be protected from adverse events, the quality of the relationship and communication between family members are important for preventing adverse longer term consequences."

When serious illness strikes, primary care clinicians have a responsibility to support the family as well as the patient.

CAFFEINE

Caffeine May Indeed Help To Keep You Awake

6-11 THE EFFECTS OF COFFEE AND NAPPING ON NIGHTTIME HIGHWAY DRIVING

Double-blind, randomized crossover study of 12 young adults, mean age 21. All had been driving for at least 2 years and drove between 10 000 and 20 000 km per year. None were professional drivers.

Compared effects on nighttime driving performance of 125 mL (half a cup of coffee) containing 200 mg of caffeine vs decaffeinated coffee (placebo) containing 15 mg caffeine given at 1:00 AM. Recorded inappropriate (center) line crossings by video during highway driving and compared self-rated fatigue and sleepiness.

Participants drove 125 miles one time between 6:00 PM and 7:30 PM (daytime reference condition); and two times between 2:00 AM and 3:30 AM (after placebo, and after caffeine). All drank the caffeine or the placebo 30 minutes before the nighttime drive.

Participants were instructed to maintain a constant speed of 80 miles per hour on a straight highway, and to drive in the center of the lane and not cross the painted lines.

After the intervention, participants returned to the laboratory to sleep and polysomnographic study.

Line crossings during daytime were infrequent. Line crossings at night after caffeine were equally infrequent. After placebo, line crossings at night were frequent.

Coffee containing caffeine at night reduced driving impairment without altering subsequent sleep.

Admittedly, a surrogate outcome, but, I believe a reasonable one. There must be a variation in response to caffeine between individuals. Some say that drinking caffeinated coffee in the evening keeps them awake. Some say no effect on sleep.

CARDIOVASCULAR DISEASE

Does a High Intake of Chocolate Reduce Risk of Death?

2-12 COCOA INTAKE, BLOOD PRESSURE, AND CARDIOVASCULAR MORTALITY

This study estimated intake of cocoa from the habitual consumption of cocoa-containing foods, and evaluated whether intake was inversely related to BP and CVD and all-cause mortality in a cohort of elderly men.

Used data of 470 elderly men (mean age at baseline = 72). All were free of chronic diseases at baseline (1985).

Assessed habitual food consumption by dietary history at 5-year intervals. This included consumption of cocoa-containing foods. Chocolate confectionary contributed about 2/3 of the total cocoa intake.

Ascertained causes of death during 15 years of follow-up.

Mean blood pressure highest tertile of cocoa use vs lowest tertile of use:

A. Mean systolic was 3.7 mmHg lower.

B. Mean diastolic was 2.1 mmHg lower.

	Tertiles of cocoa intake		
	Lowest (0.5 g/d)	Middle (0.5-2.25 g/d)	Highest (> 2.3 g/d)
No of subjects	165	149	156
Cocoa median g/d	0	0.92	4.2

Relative risk (RR) of death:

A Cardiovascular death (CVD): highest tertile compared with lowest tertile of cocoa use = 0.50.

B. All-cause mortality: highest tertile vs lowest tertile of cocoa use = 0.53.

(These RRs resulted from a model which adjusted for 19 possible confounders. RTJ)*

"In the present study, usual daily cocoa intake was inversely related to blood pressure."

"In prospective analysis, usual cocoa intake was associated with a 45% to 50% lower risk of cardiovascular and all-cause death."

The results are provocative, but unrealistic. I doubt the investigators really believe that cocoa is related to a 50% reduction in mortality. The observational study assumed many adjustments for possible confounding variables. It followed a relatively small number of subjects.

I can visualize a report in the lay press—"Chocolate reduces risk of death by 50%". Conflicting reports of medical studies result in an increasingly skeptical public.

If You Can't Lose Weight, at Least Get in Better Physical Shape.

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The main message for primary care might be—If you can't lose weight, at least get in better shape physically. It would be better, however, if you lose weight and get in better shape.

It is very unlikely that an overweight or obese person will lose weight and maintain the loss with diet alone. A combination of calorie restriction and increased physical activity is required.

4-1 TRANS FATTY ACIDS AND CARDIOVASCULAR DISEASE: Review Article

Trans fats are formed during "partial hydrogenation" of vegetable oils (an industrial process). This converts the oil into semisolid form for use in margarines, commercial cooking, and manufacturing processes. The food industry favors trans fats because their shelf life is long, they are stable during deep-frying, and may enhance palatability of baked goods and sweets.

The average consumption of trans fats in the USA is 2% to 3% of total calories consumed.

The Department of Agriculture made limiting intake of trans fats a key recommendation in the new food pyramid. Consumption should be limited to below 1% of total energy intake.

The FDA has ruled that the nutrition labels of conventional foods and supplements must indicate the content of trans fats. (*Consumers should remember to check the "Nutrition Facts' on labels. RTJ*)

These actions were prompted by evidence that trans fats increase the risk of coronary heart disease by several different mechanisms:

A. Adverse effect on serum lipids.

B. Promotion of systemic inflammation.

C. Trans fats may also cause endothelial dysfunction.

"On a per-calorie basis, trans fats appear to increase the risk of CHD more than any other macronutrient." Even at low levels of consumption (1 to 3 percent of calories), a substantially increased risk occurs.

Trans fats have no intrinsic health value above their caloric value. Thus, their intake may result in considerable potential harm with no apparent benefit.

The potential harm is clear. Adverse effects are seen even at low intakes—1% to 3% of total energy

(~ 20 to 60 calories; 2 to 7 grams for a person consuming 2000 calories daily).

"Thus, complete or near complete avoidance of industrially produced trans fats—consumption of less than 0.5 percent of total energy intake—may be necessary to avoid adverse effects."

Avoidance will depend on consumers' decisions to choose foods free of trans fats. This depends on knowledge of the type and quantity of oils used. *(Again, read the label. In restaurants, choose foods less likely to contain trans fats. RTJ)*

About 20% of CHD events could be prevented by total avoidance of trans fats and replacement with cis unsaturated fats.

Elimination of trans fat (as much as possible) should be considered a major goal for reducing risk of CHD. Obviously, daily consumption of 2 grams (over 1% of total calorie intake) is very easy.

Fifty Percent of The Servings Contained More Than 5 Grams Per Serving—The Amount Associated With A 25% Increase in Risk Of Ischemic Heart Disease

4-2 HIGH LEVELS OF INDUSTRIALLY PRODUCED TRANS FAT IN POPULAR FAST FOODS

"The daily intake of about 5 grams of trans fats is associated with a 25 percent increase in the risk of ischemic heart disease."

This study determined the content of industrially produced trans fat in fast foods purchased in 2004 and 2005 in 20 countries. The table (p 1651) illustrates the amounts of trans fat in McDonald's and KFC outlets in a large serving of french fries and chicken.

The content of trans fat in a large serving of french fries varied from less than 1 gram in Denmark to 7 grams in New York City and 12 grams in Hungary. Fifty percent of the servings contained more than 5 grams—the amount of daily intake associated with a 25% increase in risk of ischemic heart disease.

Large variations were observed within the same chain in the same country.

As the general public becomes more aware to the risks, I believe that fast food companies and food manufacturers can (and may have to) lower the trans fat content of their foods. The fact that the trans fat content varies markedly in different countries and even within a given country suggests that consumers will accept foods prepared with oils containing lower amounts of trans fats.

McDonalds is trying. I recently picked up several brochures describing their efforts to promote balanced eating. Their "McDonald's Nutrition Facts" lists foods prepared with "partially hydrogenated" cooking oils.

Tables list trans fat content	*Grams*
Plain hamburger	*0.5*
Big Mac	*1.5*
Small french fries	*2.5*
Large french fries	*6.0*
Biscuit	*5.0*
Deluxe breakfast	*11*

Warm cinnamon roll *4.5*

Baked apple pie *4.5*

Chocolate chip cookie *1.5*

I enjoy McDonalds and KFC. I believe they will attempt to lower trans fat content. I will watch developments carefully, while I avoid ingestion of trans fats as much as possible.

CHOLESTEROL

"Adverse Effects Of Statins are Underreported, and Benefits of Higher Doses May Be Exaggerated."

6-4 SHOULD WE LOWER CHOLESTEROL AS MUCH AS POSSIBLE?

The National Cholesterol Education Program suggests that persons at high risk of cardiovascular disease should be treated more aggressively. "Aggressive" means that LDL-cholesterol levels should be lowered to less than 70 mg/dL (1.81 mmol/L). This recommendation, if strictly followed, would put most of the Western world's adult population on statin therapy.

These editorialists believe the benefit/risk ratio of more drastic lowering of LDL-c is not known. They question the wisdom of this advice. They believe the adverse effects of statins are underreported in clinical trials, and that benefits of higher doses may be exaggerated.

I believe patients and primary care clinicians have focused too exclusively on cholesterol levels, and consider it the major risk factor for cardiovascular disease, while ignoring other risk factors which are equally important.

Statins may reduce risk to a minor extent in smokers, but high risk remains. One might ask—what is the benefit of lipid control if the patient continues to smoke? The same applies to poorly controlled hypertension, diabetes, obesity (especially abdominal obesity), and sedentary lifestyle.

Conversely, for patients without risk factors other than LDL-c, I believe that lowering it to below 70 is not likely to materially improve prognosis unless LDL-c is excessively high.

Remember that most satins are metabolized in the liver by the cytochrome P450 system, and thus are liable for interactions with other drugs.

The adverse effects of statins are likely underreported. High doses are related to a greater number of adverse effects. I believe in a general rule: Adverse effects of drugs are more related to dose than to idiosyncrasy. Start with what is defined as the standard dose (or lower, especially in the elderly whose creatinine clearance gets lower with age, and in patients with renal and liver disease). If a standard dose does not result in the desired effect, adding a second and a third drug will likely be safer than increasing the dose of the first drug.

Cost is also an important factor. Patients should be told they can save hundreds of statin dollars yearly if they choose a low cost generic statin, buy a $3 pill cutter, and purchase the high dose pills and cut them to the desired dose. Statins have a high therapeutic index.

I also believe that generic statins (eg, Simvastatin) will provide about as much protection as other statins if other risk factors are treated at the same time and if the dose is adjusted.

We have also failed to fully implement dietary measure to control lipids.

COCOA

Does a High Intake of Chocolate Reduce Risk of Death?

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COLONOSCOPY

Screening The Very Elderly Results In Only 15% Of The Expected Gain In Life Achieved In Younger Persons.

5-7 SCREENING COLONOSCOPY IN VERY ELDERLY PATIENTS

Although the prevalence of colonic neoplasia increases with age, the benefits of screening (and removal of adenomas and cancers) in the elderly may be limited in part because very elderly patients have short life expectancies.

This study compared estimated life-years saved with screening colonoscopy in elderly patients vs younger patients.

A statistical analysis calculated life expectancy based on several conditions:

A. If no neoplasm found

B. If a neoplasm was found and removed

C. If a neoplasm was present but not removed

D. Expected years lived during polyp lag time (time for adenoma to change into cancer).

E. Life expectancy after cancer diagnosis.

Compared life expectancy of each screened patient with the life expectancy of that same patient if he or she had not been screened.

Age	50-54	75-79	80 and over
Remaining life expectancy (mean y)	29	10	8

In the over 80 age group, gain in mean life expectancy was much lower than in the 50-54 age group. (0.13 years vs 0.85 years). This was despite the greater frequency of neoplasia in the older group.

The main target of colonoscopy screening is detection and removal of adenomas. There is a long lag time before adenomas can develop into cancer and cause death. In very elderly persons, the potential benefit of removal of an adenoma may be smaller than in younger patients because the elderly die of other causes before the adenoma can develop into cancer.

Although the prevalence of colonic neoplasia increases with age, colonoscopy screening in the very elderly results in only 15% of the expected gain in life achieved in younger persons.

“Screening colonoscopy in very elderly patients should be performed only after careful consideration of potential benefits, risks and patient preferences.”

By definition, screening, pertains to asymptomatic patients. Outcomes will differ in those with symptoms.

Obviously, we have to stop screening sometime. When depends on the individual. Some elders are more vigorous than others and have a longer life expectancy. Some fear cancer and welcome the reassurance of a negative colonoscopy. Some have prior adenomas and a family of colorectal cancer.

The article outlines some additional problems with colonoscopy in the very elderly. I would be wary of adverse effects of anesthesia (including “conscious” anesthesia) on cognition of older patients.

There should be restraint in screening the elderly.

COFFEE

Caffeine May Indeed Help To Keep You Awake

6-11 THE EFFECTS OF COFFEE AND NAPPING ON NIGHTTIME HIGHWAY DRIVING

Double-blind, randomized crossover study of 12 young adults, mean age 21. All had been driving for at least 2 years and drove between 10 000 and 20 000 km per year. None were professional drivers.

Compared effects on nighttime driving performance of 125 mL (half a cup of coffee) containing 200 mg

of caffeine vs decaffeinated coffee (placebo) containing 15 mg caffeine given at 1:00 AM. Recorded inappropriate (center) line crossings by video during highway driving and compared self-rated fatigue and sleepiness.

Participants drove 125 miles one time between 6:00 PM and 7:30 PM (daytime reference condition); and two times between 2:00 AM and 3:30 AM (after placebo, and after caffeine). All drank the caffeine or the placebo 30 minutes before the nighttime drive.

Participants were instructed to maintain a constant speed of 80 miles per hour on a straight highway, and to drive in the center of the lane and not cross the painted lines.

After the intervention, participants returned to the laboratory to sleep and polysomnographic study.

Line crossings during daytime were infrequent. Line crossings at night after caffeine were equally infrequent. After placebo, line crossings at night were frequent.

Coffee containing caffeine at night reduced driving impairment without altering subsequent sleep.

Admittedly, a surrogate outcome, but, I believe a reasonable one. There must be a variation in response to caffeine between individuals. Some say that drinking caffeinated coffee in the evening keeps them awake. Some say no effect on sleep.

CONGENITAL ABNORMALITIES

Angiotensin II Blockers as Well

6-12 ACE INHIBITORS AND CONGENITAL ABNORMALITIES

When ACE inhibitors (**ACE**; eg, *Captopril*; the prototype) are used in the second half of pregnancy, they can cause major congenital abnormalities. These effects result from blockade of conversion of angiotensin I to angiotensin II in the developing fetal kidneys. A similar pattern has been reported after treatment with angiotensin II- receptor-antagonists.

A study in this issue of NEJM reports that major congenital abnormalities may also occur if ACE are taken during the *first* trimester of pregnancy.

All drugs are foreign to the body. All drugs should be avoided in pregnancy. This essentially means that all women of child-bearing age should avoid drugs unless they are considered essential, or it is established without a doubt that they will not become pregnant. No tobacco; no alcohol; no drugs.

Almost half of all pregnancies are unintended.

Primary care clinicians must be among the major prescribers of ACE. Acting on this information may prevent a major catastrophe.

CORONARY HEART DISEASE

No Benefit; No Harm

2-5 CONJUGATED EQUINE ESTROGENS AND CORONARY HEART DISEASE *The Women's Health Study*

Recent randomized trials of hormone replacement therapy (**HRT)** with conjugated equine estrogens (CEE) + medroxyprogesterone reported no protection against coronary heart disease **(CHD),** and may have increased risk.

This associated, but separate, trial considered women who had experienced a hysterectomy and were eligible to receive unopposed CEE . This is the final report of the trial.

Randomized over 10 000 women (mean age = 64) to; 1) unopposed CEE 0.625 mg daily, or
2) placebo.

At 7 years, 201 coronary events occurred in the CEE group, vs 217 in the placebo group. (No clinical or statistical difference.)

This study is important. It applies to the many women who have undergone hysterectomy whose menopausal symptoms are disturbing. It was reported without editorial comment as the last article in this issue of Archives. I believe it deserved wider distribution. Estrogens-alone did not lead to excess CVD risk.

Observational studies long reported that HRT protected against cardiovascular disease. This, it finally turned out, was due to the bias of the "healthy user".

The original reports of WHI studies [1,2] *(CEE + progestin) were widely distributed and caused much comment. They refuted the long-held view that HRT would protect against cardiovascular disease. The main conclusion was that HRT should not be used to prevent CVD.*

Many doctors then discontinued prescribing CEE + progestin. And many women stopped taking it (despite continuing menopausal symptoms), and despite the low excess risk of cardiovascular events over 5 years.

4-11 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN PATIENTS WITH CORONARY HEART DISEASE AND ABSENCE OF HEART FAILURE OR LEFT VENTRICULAR SYSTOLIC DYSFUNCTION

"Angiotensin-converting enzyme inhibitors (**ACE**) . . . **"**are an undisputed treatment in patients who have congestive heart failure **(HF),** or in patients with coronary heart disease **(CHD)** and concomitant left ventricular dysfunction."

This meta-analysis assessed long-term effects of ACE in patients who have CAD and no signs of HF or severe left ventricular dysfunction. (Stable coronary artery disease.)

Treatment ACE inhibitors included ramipril, quinapril, enalapril, perindopril, and trandolapril.

Overall results:	Active treatment	Placebo	Absolute difference	NNT (4-y)
	n = 16 328 (%)	n = 16 034 (%)	(% in 4.4 years)	
All-cause death	1215 (7.4)	1392 (8.7)	1.3	77
CV death	673 (4.1)	819 (5.1)	1.0	100
MI	1048 (6.4)	1258 (7.8)	1.4	71

Stroke	342 (2.0)	445 (2.7)	0.7	142

Use of ACE inhibitors for long-term secondary prevention in patients with established CHD, who are without LV dysfunction or heart failure, was associated with a reduction in all-cause mortality and major cardiovascular events.

Note that elevated BMI, smoking, hypertension, and dyslipidemia were present in many patients at baseline. The study did not consider influence of these factors on outcomes. Apparently, many of these factors were not treated or were under treated. The study concentrated on taking a pill or not taking a pill.

I believe correcting these risk factors would improve prognosis much more than taking a pill once a day.

What about cost? My pharmacy quotes $2.23 for one 10-mg ramipril (Altace). This would cost the patient about $3260.00 over four years. You may ask. . . "Would you pay over $3000.00 for a one in 100 chance of avoiding death from a cardiovascular cause over 4 years? And at the same time incurring considerable adverse effects from the drug?

Moderate Alcohol Consumption Reduces Risk of CHD in Middle-Age

5-6 PROSPECTIVE STUDY OF ALCOHOL DRINKING PATTERNS AND CORONARY HEART DISEASE IN WOMEN AND MEN

Prospective epidemiological studies have reported a lower risk of coronary heart disease **(CHD)** among consumers of *moderate* amounts of alcohol as compared with abstainers. Results consistently imply that the pattern of drinking is important, and that steady (eg, daily; several times a week) drinking is beneficial.

This study determined the association between drinking patterns and CHD among middle-aged men and women.

The amount of alcohol intake was inversely associated with CHD among *both* men and women. Adjusted hazard ratio of CHD *decreased* progressively in a graded manner as number of drinks per week *increased* from 0 to 7, to 14, and to >28 in women and to > 35 in men.

Among men, drinking frequency (days per week), not amount of alcohol intake, seems more important in reducing risk of CHD. Among women, alcohol intake (total amount per week) may be the primary determinant of the inverse association.

It may be that heavy drinkers and abusers of alcohol have less risk of CHD than abstainers and moderate drinkers. The risks of heavy drinking far outweigh any benefit.

Some commentators recently have doubted the association between frequent and moderate alcohol consumption and reduction in risk of CHD. I believe the important message of this study is a confirmation of previous studies reporting benefit of reducing risk of CHD (for both men and women) who drink frequently but moderately. Women (and men) who binge drink are obviously at great risk of adverse effects of alcohol. Whether this reduces risk of CHD is irrelevant.

I do not believe the observation that amount of drinking in women confers less risk of CHD is clinically important. Frequency of moderate drinking in women (as in men) is associated with lower risk of CHD, and may

be clinically important. I believe the same advice pertains to women and men (and physicians as role models): If you wish to drink, and enjoy drinking, have one drink before dinner, or one glass of wine with dinner.

CYCLO-OXYGENASE-2 INHIBITORS (COX-2)

All, Except Possibly Naproxen, Carry Some Risk of Atherothrombosis.

6-2 DO SELECTIVE CYCLO-OXYGENASE-2 INHIBITORS AND TRADITIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INCREASE THE RISK OF ATHEROTHROMBOSIS?

A Meta-analysis of Randomised Trials

. This meta-analysis included 138 randomized trials comparing selective COX-2 inhibitors versus 1) placebo, and 2) traditional non-selective NSAIDs. All studies included information about serious vascular complications (myocardial infarction [**MI**], stroke, and vascular death).

Selective COX-2 inhibitors vs placebo:

An increased risk associated with the former (1.2% per year vs 0.9% per year) [Absolute difference = 0.3%; NNT to harm one patient over 1 year = 333.]. This was chiefly attributed to an increase in risk of MI (0.6 per year vs 0.3 per year) with little apparent difference in other vascular outcomes.

"There was no significant heterogeneity among the different selective COX-2 inhibitors."

Traditional NSAIDs versus placebo:

	Rate ratio for vascular events
Naproxen vs placebo	0.92 (Ie, less risk than placebo)
Ibuprofen vs placebo	1.5
Diclofenac vs placebo	1.6

Selective COX-2 inhibitors vs traditional NSAIDs:

Overall, there was no significant difference in incidence of serious vascular events between 1) selective COX-2 inhibitors and 2) traditional NSAIDs—340 vascular events during over 33 000 person years of exposure to 1), and 211 vascular events in over 22 000 person-years of exposure to 2). [1% per person-years vs 0.9% per person-years.

Selective COX-2 inhibitors were associated with a 1.4-fold increased risk of serious vascular events largely due to a two-fold increase in myocardial infarction.

High doses of ibuprofen and diclofenac were associated with a similar increased risk.

High doses of naproxen were *not* associated with increased risk.

Traditional NSAIDs also inhibit the enzyme COX-2. If selective COX-2 inhibitors are associated with increased risk, it would seem reasonable to assume that traditional NSAIDs would also increase risk.

Do patients with higher baseline risks of MI have higher risk of MI associated with COX-2 inhibitors? If so, would not reduction of other risk factors (smoking, dyslipidemia, hypertension) reduce the risk of MI associated with COX-2 inhibitors and higher-risk traditional NSAIDs? Would it be more dangerous to prescribe NSAIDS to these patients?

All NSAIDs except naproxen (Generic; Naprosin) carry risk of atherothrombotic disease, especially when used for long periods at high doses. We should not forget that NSAIDs have adverse effects on the kidney, blood pressure and heart (increasing risk of congestive failure).

I believe the widespread acceptance and use of COX-2 inhibitors is a tribute to the marketing skills of drug companies.

"Patients Should Always Be Offered Acetaminophen Before Resorting To Other Analgesics."

6-3 LIFE WITHOUT COX-2 INHIBITORS *Doctors Need To Broaden Their Approach To Pain In Older Patients*

Several selective COX-2 inhibitors have been withdrawn from the market. Use of others is being limited because of increased risk of myocardial infarction in long-term users.

"Have we lost a truly superior option? Probably not. Other pharmacological and non-drug options may be reasonably effective, equally safe, and less costly."

Acetaminophen (eg, *Tylenol*) offers effective and safe treatment for general musculoskeletal pain, including osteoarthritis. "Patients should always be offered acetaminophen at sustained doses before resorting to other analgesics." It has a relatively high safety margin except in overdose. It should be limited to 4 g daily, and less if the patient has liver disease or has high alcohol intake.

Opioids can be used as a last pharmacological resort. "Concerns about addiction are largely unfounded." Dependence—withdrawal symptoms if drugs are withdrawn—can be expected. "Fear of dependency and addiction is not sufficient justification to fail to relieve pain."

The editorialists comment on other pain-relieving measures: topical diclofenac; braces; exercise; glucosamine.

"Rather than lamenting the loss of COX-2 inhibitors—an intervention more popular than proved—we will best serve our patients by thinking creatively about other approaches to their pain." Presenting a menu of possible treatments and working with patients to choose those that best suit their lifestyle and health beliefs is the optimal way to find solutions to their chronic pain.

Some drugs are available combined with acetaminophen. Many variations are available allowing for personal choice. None offers complete relief. All have some degree of placebo effect.

I believe most older people with osteoarthritis pain accept, and live with some degree of discomfort. Many go on to consider joint injections and replacement therapy.

CT SCAN

Danger, Especially From Repeated CTs

5-12 HEALTH EFFECTS OF IONIZING RADIATION FROM DIAGNOSTIC CT

An estimated 60 million computerized tomographies (CTs) were done in the USA in 2002. This represents 70% of all medical X-ray exposure.

The National Academy of Science report on the Biological Effects of Ionizing Radiation indicated that a single population dose of 10 mSv is associated with a lifetime attributable risk of developing a solid cancer or leukemia is 1 in 1000. The typical abdominal examination dose is between 10 and 20 mSv. The breast glandular dose during a pulmonary artery CT angiogram is 20 mSv.

"The ionizing radiation exposure from a single abdominal or chest CT may be associated with elevated risk for DNA damage and cancer formation." The radiosensitive tissues are predominantly within the field of view of common chest, abdominal, and pelvic CT scans.

Many patients are exposed to multiple examinations that increase cumulative dosing. One subset of patients with renal colic had total exposure rates between 19 and 154 mSv.

Referring physicians are largely unaware of the potential harmful effects from CT radiation exposure. Radiologists doing CT examinations consider the radiation exposure of limited concern. "Many are unaware of the dose of radiation delivered to the patient." The risk may not be explained clearly to patients before obtaining consent.

Radiation effects may not manifest until 5-20 years after exposure. Causal relations are not apparent on an individual basis.

The editorialists suggest some means by which exposure can be limited, including greater use of MRI.

I do not know enough about radiation physics to comment. I hope some radiologists will respond.

I believe the caution is appropriate. I abstracted the editorial because primary care clinicians often refer patients for CT. They bear some responsibility for the cumulative doses of radiation.

Commercial entrepreneurs continue to offer unselected CT screening, including whole body screening, to the general public. Some clinicians are enthusiastic about CT screening for coronary artery calcification. I believe there is little concern about radiation exposure.

I believe the scanning procedure used depends on the equipment available in the community and the expertise of the radiologist.

DEPRESSION

"All Screening Programs Do Harm; Some Do Good As Well"

4-7 SHOULD WE SCREEN FOR DEPRESSION? A Review of Screening Programs

This article presents 9 key criteria of UK National Screening Committee for screening.

(Read the abstract and the article. RTJ)

For screening for depression, the article concludes: "Opportunistic screening and population level screening for depression do *not* fulfill the criteria of the UK Screening Committee."

The use of these criteria indicates that screening for depression is unlikely to be a clinically effective or cost effective way to improve the mental wellbeing of the population. Screening alone cannot improve the management and outcome of depression unless systems to manage the depression are available.

I believe this presents an important consideration for primary care. The criteria considerably restrict screening.

Strictly defined, screening applies only to persons who have no signs or symptoms of the condition in question. This implies that the condition screened for, in the population selected, reflects only the prevalence of that condition in that population.

The borderline between screening and testing is ill defined.

I believe that most screening in primary care practice is applied to persons who have at least some pre-test probability of having the condition screened for. The "screen" then becomes a "test". A positive result would indicate a higher post-test probability of having the condition.

I believe screening in the USA is overdone. Primary care clinicians should be circumspect. They should make the patient aware of risks (including creation of considerable ongoing anxiety) as well as benefits of a screen. The patient should be willing to proceed to further investigation and treatment if the screen is positive. Adequate referral and treatment should be available.

I note that some entrepreneurs still come to town offering "Life Line Screening". All residents are invited to participate. The screens (for a fee) include "stroke/carotid artery screening, abdominal aortic aneurysm screening, and peripheral artery disease screening". This type of screening meets few of the UK National Screening Committee key criteria. I believe they do more harm than good.

DIABETES

Obesity Per Se In Middle Age Is A Risk Factor For CVD And Diabetes In Older Age

1-4 MIDLIFE BODY MASS INDEX AND HOSPITALIZATION AND MORTALITY IN OLDER AGE

Does excess weight in middle life confer higher risk of cardiovascular disease (**CVD**) and diabetes in older age? Does a high body mass index (**BMI**) *per se* confer risks over time independent of its effect on BP and lipids?

This prospective study, begun in 1967-73, entered over 17 000 subjects age 31 to 64 (mean age = 45). All were free of coronary heart disease **(CHD)** , diabetes, and major electrocardiography abnormalities.

At baseline, classified CVD risk as: 1) Low risk: BP < 120/80; total cholesterol < 200; and non smoking. 2) Moderate risk: BP 121-139/81-89; total cholesterol 200-239; non smoking; 3) Higher risk groups included subjects with any 1, 2, or 3 risk factors (BP > 140/90; total cholesterol > 240; and current smoking.

BMI categories: normal 18.5-24.9; overweight 25-29.9; obese 30 and over.

At baseline, only 7% of the entire cohort over 17 000 were at low risk. And only 4% were at both low risk and normal BMI.

Low risk group: (normal BP, normal cholesterol, and non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes
Normal BMI	30	40	44
Overweight	42	49	110
Obese	44	112	265

Moderate risk group: (moderately elevated BP and cholesterol, non-smoking)

Rate after age 65 per 1000 persons	CHD mortality	Hospitalization for CHD	Diabetes

Normal BMI	42	53	60
Overweight	49	95	122
Obese	89	104	240

In higher risk groups (including smokers) as BMIs rose, outcomes rose in a similarly graded fashion. Within each risk stratum, the risk was higher for overweight and obese persons than for normal weight persons.

Non-smoking individuals with normal BP and normal total cholesterol who are obese in middle age have a higher risk of hospitalization and mortality from CHD and diabetes in older age than those whose weight is normal in middle age. This risk relationship extends to those with higher cholesterol and BP and to those who smoke.

Clinical Review: "Approaches Are Available That Promote Successful Management" And a Peek into the Future

4-4 ASSESSING GLYCEMIA IN DIABETES USING SELF-MONITORING BLOOD GLUCOSE AND HEMOGLOBIN A_{1C}

Self-monitoring blood glucose **(SMBG)** reveals the immediate hour-to-hour glucose, which normally varies only about 50% throughout the day, but may vary 10-fold in patients with diabetes. It shifts the focus of diabetes management from the doctor's office into the hands of the patient. It allows patients to take control of their own diabetes.

This systematic literature search assessed the evidence underlying the use of SMBG, and HbA1c. It considers:

SMBG:

Does SMBG positively affect patient care?

How often to test?

Goals of testing

Optimal timing

Future clinical applications

HbA1c:

How effective is reduction ?

Standardization

Use for screening for diabetes

New certified rapid assay

Future clinical applications.

Read the abstract.

I believe SMBG and HbA1c levels are useful and rewarding applications. It depends on how they are used. Proper use depends on close patient-health professional cooperation. There is a learning curve. I believe individualization is the key.

"When Added To Oral Agents, It May Obviate The Need For Insulin Injections Entirely".

5-5 INHALED INSULIN

In January 2006. the FDA approved the first inhaled insulin for treatment of both type 1 and type 2 diabetes (**DM-1** and **DM-2**).

For DM-1, inhaled insulin is likely to be accepted by both the public and the medical community. "It is perhaps surprising how frequently individuals with longstanding type 1 diabetes, who have adapted to multiple daily injections, are excited by the potential of needing only a single, long-acting insulin injection daily, with inhaled insulin replacing pre-meal injections.

For DM-2, the market for inhaled insulin is more complex. Newer, oral agents are under development. Insulin, regardless of route of administration, is the most potent glucose-lowering therapy. It has been used for 80 years. Its side effects are well known. Inhaled insulin has the potential to be beneficial in the long run.

Expense may be a problem for many.

This editorial lists 12 clinical points Read the full abstract

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The editorialist seems to be enthusiastic. Among patients for whom cost is no problem, I believe many will welcome and use inhaled insulin. Worldwide, for the great majority of patients with diabetes, cost will prohibit use.

DIET

Do Wine Drinkers Have A More Healthy Diet?

3-6 FOOD BUYING HABITS OF PEOPLE WHO BUY WINE OR BEER

This study investigated whether people who drink wine buy healthier foods than people who drink beer.

Obtained data from 3.5 million transactions in Danish supermarkets; 5.8% of customers bought wine but no beer; 6.6% bought beer, but no wine; 1.2% bought both.

Compared 40 categories of food bought by wine purchasers *vs* beer purchasers.

Wine buyers bought more olives, fruit, vegetables, poultry, cooking oil, and low fat cheese.

Beer buyers bought more ready cooked dishes, sugar, cold cuts, chips, pork, butter, margarine, sausages, lamb, and (especially) soft drinks.

Wine buyers were more likely to buy "Mediterranean" diet food items; beer buyers more likely to buy "traditional" food items.

Wine tends to be drunk with meals, in modest amounts. This may have metabolic advantages.

The reported influence of type of alcoholic drink on mortality could be due to insufficient adjustment for lifestyle factors.

The "French paradox" indicates that the high consumption of wine in France (and its protective effect) more than overcomes the harmful effects of fatty foods (which the French people presumably eat in high quantities).

Epidemiological studies indicate a strong protective effect of modest daily alcohol consumption on risk of coronary heart disease. Whether wine (specifically red wine) is responsible has been debated. Some studies report that the type of alcohol is not relevant.

Epidemiological studies contain many confounders. In regard to the protective effect of wine, the accompanying type of diet must be a major confounder.

A recent meta-analysis (comment on by BMJ April 8, 2006; 332: 811) suggests that the epidemiological findings of the putative protective effect of alcohol maybe in error because the control groups (abstainers) were misclassified. Many "abstainers" were really persons who had stopped drinking because of ageing or ill health. This resulted in an increase in death among "abstainers" which was misinterpreted to be due to a lowering of death in the drinkers.

Modest intake of wine is an essential component of the healthy Mediterranean diet.

DYSPEPSIA

Eradication Results in Modest Improvements in Patients with Dyspepsia

1-10 IMPACT OF HELICOBACTER ERADICATION ON DYSPEPSIA, HEALTH RESOURCE USE, AND QUALITY OF LIFE; The Bristol Helicobacter Project.

This study determined the impact of a community-based *H pylori* screening and eradication program on incidence of dyspepsia.

A program in 7 general practices screened over 10 500 unselected individuals for *H pylori*. About 25% had dyspepsia. All were screened by a ^{13}C urea breath test. 15% were positive. Of these, 1558 were randomized to a 2 week course of 1) eradication treatment with ranitidine bismuth citrate and clarithromycin, or 2) placebo.

Followed for up to 2 years for rates of primary care consultations for dyspepsia to determine if eradication influenced subsequent dyspepsia.

Treatment eradicated 91% of the infections.

Subsequently consulted for dyspepsia over the subsequent 2 years:

Treated group 55/787 = 7/100

Placebo group 78/771 = 10/100

Number needed to treat to avoid one subsequent consultation for dyspepsia = 33.

As the investigators suggest, a trial entering only patients with dyspepsia (rather than patients selected from the general population) would likely yield a greater benefit from treatment. .

In general, treatment of the infection in patients with functional dyspepsia associated with H pylori will relieve the symptom in about 5% to 10%. Whether to test and treat depends on negotiations between patient with dyspepsia and physician. The patient may be told that eradication will cure and prevent peptic ulcer, and prevent some gastric cancers. The downside would be the cost and possible adverse effects of eradication treatment. And the likely increase in resistance of the organism to clarithromycin.

The study presents a good estimate of the percentage of free-living persons in the community who have the infection (~5% to 10%). I suspect the percentage is similar in the USA.

I suspect that, patients presenting to primary care with prolonged and troublesome dyspepsia will most likely be asked to consider endoscopy first. This would relieve anxiety and lead to more definitive therapy. If the outcome were functional dyspepsia, a "test and treat" approach would lead to reduction in symptoms in a minority of patients.

END OF LIFE CONCERNS

One Simple Non-Threatening Question To Probe Spiritual Concerns At The End Of Life.

1-1 ARE YOU AT PEACE?

Acknowledging the importance of emotional and spiritual issues at the end of life is an important component of compassionate and comprehensive palliative care. Some physicians may question the appropriateness of their role in probing patients' spiritual distress, as well as the practicality of addressing such issues in the time-limited setting of usual practice. Yet, a patient's spirituality often influences treatment choices, and endows personal resources during serious illness.

Respondents (n = 248) completed several questionnaires which assessed quality-of-life at the end of life. All had advanced cancer, severe heart failure, severe COPD, or renal failure.

Examined distributions of several religious and non-religious alternative wordings—"at peace with God"; "at peace with my personal relationships"; "at peace with myself". To promote inclusiveness, the final wording was the simple question--"Are you at peace?"

Ninety % agreed with the importance of "coming to peace with God". Ranked equally, and as most important, "freedom from pain" and "being at peace with God". Items measuring peacefulness correlated highly with having a chance to say goodbye; with making a positive difference in the lives of others; giving others gifts and wisdom; sharing deepest thoughts; and having a sense of meaning in life.

Feeling at peace was strongly correlated with emotional and spiritual well-being.

"The results of this study suggest that the concept of patients' sense of being at peace may be a point in which to initiate a conversation about emotional and spiritual concerns in a non-threatening manner."

Spirituality has been defined as the search for the ultimate meaning and purpose of life. This often involves a relationship with the transcendent. Emotional and spiritual well-being underpin the broadly worded construct of "being at peace".

Patients' end-of-life experiences are constructed by multidimensional layers of relationships of physiological and biochemical processes, cognitive understandings, interpersonal connections, and bonds to the transcendent.

Asking patients about the extent to which they are at peace may offer a gateway to assessing spiritual concerns. Although these issues may be heightened at the end of life, it may influence medical decisions throughout a lifetime of care.

Read the original!

Being at peace is important at all phases of life. Asking a non-terminal 30-year old if he is at peace may lead to introspection and benefit.

ESTROGEN

No Benefit; No Harm

2-5 CONJUGATED EQUINE ESTROGENS AND CORONARY HEART DISEASE *The Women's Health Study*

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Many doctors then discontinued prescribing CEE + progestin. And many women stopped taking it (despite continuing menopausal symptoms), and despite the low excess risk of cardiovascular events over 5 years.

FDA NEW LABELING REGULATIONS

"Include A Regulatory Time Bomb"

6-6 THE FDA'S NEW LABELING REGULATIONS: Highlights and A Hidden Hazard

The FDA is trying to make the official descriptions (package inserts, or labeling) of prescription drugs—which are notoriously user-hostile—more helpful. Labeling constitutes the formal, government-approved definition of a drug's benefits and risks. They are written by the manufacturer and require FDA approval.

The FDA has announced new rules to go into effect on June 30, 2006. It is hoped that the changes will simplify the prescribing process for physicians, decrease medication errors, and improve patient safety. The new rules will require manufacturers to add a "highlights" section at the top of the label that summarizes key information about indications, risks, and doses.

The Hidden Hazard:

The most troubling aspect of the FDA's new plan has nothing to do with providing information to prescribers. The agency used the passage of the new labeling regulations to add quietly (without opportunity

to debate) a new section to its preamble that will make it extremely difficult for anyone to bring legal action against a drug manufacturer for harm caused by one of its products which has been approved by the FDA.

I applaud this attempt at clarification. Seeking specific information about a drug in the fine print of the PDR can be irritating. All of us would welcome drug information presented in a more concise and easy-to-read labels, particularly regarding adverse effects.

I would be willing to wager that the "Hidden Hazard", the effort of a government agency in effect to change the law, will be overturned.

FONDAPARINUX

A Promising Anticoagulant. Long-Term Efficacy Not Established.

2-10 EFFICACY AND SAFETY OF FONDAPARINUX FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN OLDER ACUTE MEDICAL PATIENTS

"Most patients who die from pulmonary embolism **(PE)** as a complication of being admitted to hospital are medical patients." Around 10% of deaths are due to PE.

Fondaparinux (*Arixtra*; Glaxco SmithKline) is a synthetic, selective inhibitor of factor Xa. It effectively reduces postoperative venous thromboembolism **(VTE)** after orthopedic surgery.

This study determined the short-term efficacy and safety of fondaparinux in older, acutely ill *medical* inpatients. Randomized within 48 hours to: 1) fondaparinux, or 2) placebo.. Doses were given subcutaneously daily (2.5 mg fondaparinux or 0.5 mg saline).

A. Primary efficacy outcome *for first 15 days only*:

	Fondaparinux	Placebo
Any VTE	18	29
Proximal deep vein thrombosis	5	7
Distal deep vein thrombosis	13	22
Fatal PE	0	5
Total	18/321 (5.6%)	34/323 (10.5%)

(NNT to prevent one VTE = 20.)

B. Symptomatic VTE *up to day 32*:

	Fondaparinux	Placebo
Symptomatic deep vein thrombosis	0	0
Non-fatal pulmonary embolism	1	4
Fatal pulmonary embolism	3	7

Ten *additional* cases of PE occurred during follow-up after day 15—4 in the fondaparinux group, 6 in the placebo group. (Three in the fondaparinux group were fatal.).

Major bleeding occurred in one patient in each group. (0.2%) [1]

Two thirds of the clinically apparent events and half of the fatal PE were observed *after* the initial 6 to 14 day study period. This supports the need to evaluate extended prophylaxis in medical patients.[2]

I abstracted this article mainly to introduce what may become a major breakthrough. Two new oral Xa inhibitors are in the works.

1 *If the risk of major bleeding is indeed lower with fondaparinux, it would be a major benefit. Watch for further studies.*

2 *Note that the study focused on outcomes over 2 weeks only. The risk of VTE in these very ill older patients extends far beyond. The investigators note that VTE occurred frequently after the study period. Some were fatal. The question remains: How long must fondaparinux be continued in these medical patients? And for how long? . Duration of therapy for only 2 weeks adds relatively little overall protection.*

Reduced Deaths and Reinfarction without Increase in Bleeding A New Era in Anticoagulation?

4-8 EFFECTS OF FONDAPARINUX ON MORTALITY AND REINFARCTION IN PATIENTS WITH ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION: The Oasis-6 Randomized Trial

Despite many therapeutic advances, mortality in patients with acute ST-elevation myocardial infarction (**STEMI)** remains high. Antiplatelet therapy, thrombolysis, and angiotensin-converting enzyme inhibition improve prognosis. Primary percutaneous coronary intervention (**PCI**) offers benefits over thrombolytic therapy, but access to this procedure is limited.

Trials of unfractionated heparin, direct thrombin inhibitors, and enoxaparin (a low-molecular-weight heparin) have thus far failed to demonstrate mortality reductions. Reviparin (also a low-molecular–weight heparin) has been shown to reduce mortality and reinfarction, but bleeding is increased when it and other agents are used with aspirin and thrombolytic therapy.

This large randomized trial evaluated the effect of fondaparinux (*Arixtra*; a synthetic pentasaccharide which rapidly inhibits factor Xa) when initiated early and given up to 8 days.

One group of patients received a fixed dose of fondaparinux (2.5 mg subcutaneously daily for 8 days) or placebo; another group received fondaparinux or 2 days of unfractionated heparin + placebo.

Overall, at 30 days and at 3 to 6 months, death and reinfarction occurred less frequently in the fondaparinux group. (NNT = 66 and 70).

Benefits were evident in those receiving no reperfusion therapy and in those receiving thrombolysis. No benefit in those undergoing PCI.

Severe bleeding was less likely in the fondaparinux group. (Overall, 1.0% vs 1.3%)

“Unlike other antithrombotic agents, such as low-molecular-weight heparin, direct thrombin inhibitors, or intravenous antiplatelet agents, fondaparinux reduced death and reinfarction without increasing bleeding or hemorrhagic stroke.”

“Addition of fondaparinux to thrombolytic therapy probably represents an attractive, effective, and safe option as an initial adjunctive antithrombotic agent in STEMI in patients not undergoing primary PCI.”

I wondered if the name of the drug (ending in X) was related to its effect of factor X. Note also the X in Arixtra.

The standard dose and the reduced risk of bleeding are notable benefits.

See also "Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes" (OASIS-5 NEJM April 6, 2006; 354: 1464-75) This study compared fondaparinux (2.5 mg daily) with enoxaparin (Lovenox), a low-molecular weight heparin, in over 20 000 patients with unstable angina or myocardial infarction without ST elevation. Major bleeding occurred less frequently in the fondaparinux group. At 30 days, and long-term, mortality and morbidity favored fondaparinux.

Fondaparinux has been reported to be more effective than enoxaparin in preventing venous thromboembolism. (See Practical Pointers February 2006.)

An editorial, first author Raymond J Gibbon (NEJM April 6, 2006; 354; 1524-27) suggests that 2 specific activities of fondaparinux may be responsible for the reduced risk of bleeding: 1) inhibition of factor Xa within the clot, and 2) lack of inhibition of platelet function.

GASTRO ESOPHAGEAL REFLUX DISEASE (GERD)

Weight Gain Exacerbates Symptoms; Weight Loss May Improve Symptoms

6-8 BODY-MASS INDEX AND SYMPTOMS OF GASTROESOPHAGEAL REFLUX IN WOMEN

Gastroesophageal reflux disease (**GERD**), with hallmark symptoms of heartburn and acid regurgitation, affects up to 60% of persons some time during the course of a year, and up to 30% weekly.

This study explores more fully the relation between body mass index (BMI; weight in kg / square of the height in meters) and symptoms of GERD in women.

Of 10 545 women (mean age 66), 2310 (22%) reported having symptoms at least once a week.

Women who had frequent symptoms were more likely than women without symptoms to have a higher BMI, to have a higher daily caloric intake, and to be less active.

There was a dose-dependent relationship between increasing BMI and frequent reflux symptoms.

Odds ratio compared with "reference" BMI 20 to 22.4:

BMI	< 20	20-22.4	22.5-24.9	25 -27.4	27.5-29.9	30-34.9	≥35
Odds ratio	0.67	1.00	1.38	2.20	2.43	2.35	2.93

Women with a BMI < 20 seemed to have some protections against symptoms.

Among women who gained weight during the previous 14 years, a dose-dependent increase in risk of symptoms was observed. Those gaining a BMI of 3.5 or more increased risk of frequent symptoms by more than a factor of two.

Among women who *lost* weight during the same period, there was a *reduction* in risk of symptoms. Those losing a BMI of 3.5 or more decreased risk of frequent symptoms by more than a factor of two as compared with women who had no change in BMI.

This may be helpful to some patients. I believe we can, with some assurance, tell patients with GERD that losing weight may be one factor that relieves symptoms

GESTATIONAL DIABETES MELLITUS

Regular Physical Activity Before Pregnancy Is Associated With Lower Risk Of GDM

3-8 A PROSPECTIVE STUDY OF PREGRAVID PHYSICAL ACTIVITY AND SEDENTARY BEHAVIORS IN RELATION TO THE RISK OF GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus **(GDM)** is among the most common complications of pregnancy. It affects about 4% to 7% of pregnancies. Recently, there has been a substantial rise in incidence, in parallel with the rise in incidence of obesity and type 2 diabetes **(DM-2).** This study assessed whether pregravid physical activity is associated with risk of GDM.

This study included over 21 500 women who reported at least one singleton pregnancy between 1990 and 1998. Periodic validated questionnaires asked participants to report the amount, type, and intensity of *pre*-gravid physical activity; and sedentary behavior.

After controlling for BMI, dietary factors, and other covariates, there was a statistically significant inverse relationship between physical activity and risk of GDM.

Relative risks **(RR)** of GDM according to quintiles (lowest vs highest) of pre-pregnancy activity scores:

	1st quintile	5th quintile
Total activity		
Women , No	4377	4344
MET-hours per wk	0.2	>40
Cases, No.	312	251
RR	1.00	0.81[1]

"In this large prospective cohort study of women, prepregnancy physical activity, in particular increasing vigorous physical activity, was associated with significantly lower risk of GDM. "Brisk or striding walking, and increased stair climbing were associated with substantially reduced risk, independent of total physical activity levels and prepregnancy BMI.

Physical activity during the year before pregnancy and during adolescence are strong predictors of physical activity during pregnancy. "It is plausible that much of the benefit we observed for pregravid physical activity also reflects continued activity during pregnancy.

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1 *Reporting results in terms of relative risks, and relative risk reductions can be clinically misleading as well as clinically meaningless. The article could just as well have reported that "Exercise reduces risk of GDM by 19%." Relative risks may indicate a statistical benefit (ie, the probability that the results of the trial are due to chance may be very small), but are not helpful clinically.*

Absolute risk reductions are much more meaningful from a clinical viewpoint. The absolute benefit of the highest quintile vs the lowest quintile of total physical activity (by my calculations based on their tables) = 1.3%. (Ie, there was between 1% and 2% benefit from exercise in reducing development of GDM. I believe this is a clinical benefit. The benefit/harm-cost ratio may be very high, because, although the absolute benefit is small, the

denominator of the ratio (harm-cost of physical fitness) is nil. Women should be encouraged to maintain physical fitness before and during pregnancy.

GERIATRIC MEDICINE

3-1 RECONSIDERING MEDICATION APPROPRIATENESS FOR PATIENTS LATE IN LIFE

This article asks: For frail elderly patients, when might it be best to *discontinue* (or not prescribe) medications that are otherwise considered appropriate on the basis of guidelines? The authors propose a 4-component model to guide appropriate prescribing for patients late in life:

1) *The goals of care of the patient:* "Regardless of standards of care, practice guidelines, and other clinical pathways, shared decision making among physicians, patients, and families about goals of care is important when deciding whether to stop, start, or continue therapy with a medicine for a patient late in life."

2) *Remaining life expectancy:* Very old patients with multiple comorbidities are not likely to live longer than another few years. It might not be reasonable to apply long-term preventive care to these patients.

3) *Time until benefit:* Some medications for primary or secondary prevention take a long time to result in any benefit. Treatment with these drugs might not be started or might be discontinued in patients with limited life expectancy. The notion of *time until benefit* may be more useful in individual elderly patients than the *number needed to treat.*

4) *Treatment targets:* After goals of care have been established, the targets of the treatment must be consistent with the goals.

Ideally, each of the 4 components should be consistent with the others. This will yield a general idea of appropriate medications , and reasonable limitations. Efforts should be made to discontinue use of medications identified according to these components as inappropriate for patients late in life.

This is an important and, neglected aspect of caring for old, frail patients. It concerns the "art " of medicine much more than the "science". Indeed, there is no science to guide us in care of these patients. Guidelines are based on "evidence". For very old patients there are no randomized, controlled trials on which to base decisions. Old, frail subjects are not included in trials. Extrapolating the results of trials of younger persons to care of the elderly may be misleading and harmful.

I believe that many elderly patients take too many drugs in too high a dosage.

The first step must be to ascertain the patient's wishes. It is essential that primary care clinicians fully understand the patient's (and surrogates') wishes. This requires an unhurried consultation at which physicians explain prognosis and treatment options, seek patient goals, and, if asked, express their own opinion.

If it is too controversial to discontinue a drug, I believe it would be prudent to cut the dose in half. Frail older patients whose renal and hepatic functions are impaired will experience more adverse effects at usual doses. You may even be surprised when an "indicated" drug is withdrawn—the patient may actually feel better.

If a patient with a short life expectancy expresses a desire to have aggressive care, this goal will supercede all others, and the physician will be bound to follow an aggressive plan of treatment consistent with guidelines and ethical principles.

What about use of antibiotics if the patient develops pneumonia? I believe it is ethical and kind to withhold under some circumstances provided the patients receives adequate comfort care. What about anti-hypertension drugs; statins; low-dose aspirin; anticoagulants; hormone replacement; anticholinergics; antidepressants; bisphosphonates; Alzheimer drugs?

Like the seasoned poker player, seasoned primary care clinicians should know when "to hold" and when "to fold"? And to guide family and patient accordingly.

GLUCOSE INTOLERANCE

"Current Smoking And Exposure To Passive Smoke Were Positively Associated With Increased Risk"

5-4 ACTIVE AND PASSIVE SMOKING AND DEVELOPMENT OF GLUCOSE INTOLERANCE AMONG YOUNG ADULTS: The CARDIA Study

This prospective cohort study, begun in 1985-86 and continued for 15 years, assessed whether active and passive smokers (over 4500 men and women age 18-30 at baseline; median age = 25) are more likely to develop clinically relevant glucose intolerance or diabetes.

No subjects had glucose intolerance at baseline (defined as fasting glucose > 100 mg/dL, or taking antidiabetes drugs).

Seventeen % of participants developed glucose intolerance at fifteen years. Three % developed diabetes.

After adjustment for possible baseline confounders, there was a graded association between smoking exposure and development to glucose intolerance:

	% glucose intolerance	Hazard ratio
Current smokers	22%	1.65
Previous smokers	14%	1.17
Never smokers; passive smoke	17%	1.35
Never smokers; no passive smoke	12%	1.00

Pack-years of smoking was associated with risk of developing glucose intolerance—increasing by 18% for every increase of 10 pack-years.

Tobacco exposure was associated with development of glucose intolerance over a 15-year period with a dose-response effect. Passive smoke is a risk factor in never-smokers.

This is my first encounter with this association. This report is timely. The Surgeon General of the United States just issued a strong statement describing the dangers of passive smoke, and warning against it.

Tobacco smoke has been associated with increased risk of macular degeneration in the elderly. I do not know if there is an association with passive smoke.

GLUCOSAMINE

Combined G and C May Be Effective In the Subgroup with Moderate-To-Severe Pain.

2-9 GLUCOSAMINE, CHONDROITIN SULFATE, AND THE TWO IN COMBINATION FOR PAINFUL KNEE ARTHRITIS

This randomized, double-blind, placebo-controlled trial compared glucosamine sulfate (G), chondroitin (C), both, celecoxib, and placebo for 6 months in over 1500 patients with knee osteoarthritis.

Product selection: The study was conducted under an investigational new drug application. As such, C and G were subject to pharmaceutical regulation by the FDA. Ingredients were tested for purity, potency and quality. [1]

Primary outcome = a 20% decrease in pain from baseline to 24 weeks based on a pain score.

Overall, for all randomized patients, C and G were *not* significantly better than placebo in reducing knee pain by 20%. Change in WOMAC pain score for placebo = -86 points; for G + C = -100 points.

The rate of response to placebo was high (60% reported a decrease in pain of 20% or more). As compared with placebo, the rate of response to G was 4% higher. And the rate of response to C was 5% higher. The rate of response to both C and G combined was 10% higher. (Not statistically significant.)

Overall, response to celecoxib was 10% higher than to placebo. And response time was much faster than for C and G.

For patients with moderate-to-severe pain, the rate of response to C + G combined was significantly higher than for placebo (79% vs 54%). Change in *mean* WOMAC pain scores from baseline to end of follow=-up = -123 points in the placebo group vs -153 points in the C + G group. (Statistically significant.)

For patients with moderate-to-severe pain, G +C was associated with a *greater* reduction in pain than celecoxib: - 177 points vs - 153 points.

A 20% reduction in pain seems a very modest goal.

1 *This is unusual. Most studies of "dietary supplements" do not screen products so carefully. This study was detailed, carefully crafted, executed, and analyzed from a statistical standpoint.*

2 *Does lack of "statistical" significance preclude a prescription? I believe not. There will always be patients whose response to treatment deviates from the mean, either less favorably or more favorably. Response to C + G must be evaluated in an individual patient.*

Would I prescribe C + G for a patient with OA pain? I would prescribe acetaminophen first. In view of the safety of C +G, I would mention the combination as a possibility for the patient to consider—at least to try.

I would suggest they purchase the preparation at a national-chain pharmacy rather than by mail or on the internet. I believe it would be more likely to be as labeled.

Although primary care clinicians may not admit it, I believe many do indeed rely on the placebo effect, at least accept it when a patient reports improvement.

At my pharmacy, G (1500 mg)+ c (1200 mg) costs $32 for 120 tablets. At times, it is on sale at about half price. Celebrex 200 mg costs $ 3.19 each

GOUT

Lose Weight; Eat One Less Portion Of Meat Or Fish A Day; If You Drink, Drink Wine Instead Of Beer; Drink A Glass Of Skim Milk Daily.

6-9 DIAGNOSIS AND MANAGEMENT OF GOUT

Thirty clinical points. Read the full abstract.

HELICOBACTER PYLORI

Eradication Results in Modest Improvements in Patients with Dyspepsia

1-10 IMPACT OF HELICOBACTER ERADICATION ON DYSPEPSIA, HEALTH RESOURCE USE, AND QUALITY OF LIFE; The Bristol Helicobacter Project.

This study determined the impact of a community-based *H pylori* screening and eradication program on incidence of dyspepsia.

A program in 7 general practices screened over 10 500 unselected individuals for *H pylori*. About 25% had dyspepsia. All were screened by a ^{13}C urea breath test. 15% were positive. Of these, 1558 were randomized to a 2 week course of 1) eradication treatment with ranitidine bismuth citrate and clarithromycin, or 2) placebo.

Followed for up to 2 years for rates of primary care consultations for dyspepsia to determine if eradication influenced subsequent dyspepsia.

Treatment eradicated 91% of the infections.

Subsequently consulted for dyspepsia over the subsequent 2 years:

Treated group 55/787 = 7/100

Placebo group 78/771 = 10/100

Number needed to treat to avoid one subsequent consultation for dyspepsia = 33.

As the investigators suggest, a trial entering only patients with dyspepsia (rather than patients selected from the general population) would likely yield a greater benefit from treatment. .

In general, treatment of the infection in patients with functional dyspepsia associated with H pylori will relieve the symptom in about 5% to 10%. Whether to test and treat depends on negotiations between patient with dyspepsia and physician. The patient may be told that eradication will cure and prevent peptic ulcer, and prevent some gastric cancers. The downside would be the cost and possible adverse effects of eradication treatment. And the likely increase in resistance of the organism to clarithromycin.

The study presents a good estimate of the percentage of free-living persons in the community who have the infection (~5% to 10%). I suspect the percentage is similar in the USA.

I suspect that, patients presenting to primary care with prolonged and troublesome dyspepsia will most likely be asked to consider endoscopy first. This would relieve anxiety and lead to more definitive therapy. If the outcome were functional dyspepsia, a "test and treat" approach would lead to reduction in symptoms in a minority of patients.

HERNIA

Is Watchful Waiting A Safe And Acceptable Option?

1-5 WATCHFUL WAITING VS REPAIR OF INGUINAL HERNIA IN MINIMAL SYMPTOMATIC MEN

Patients often delay hernia repair until pain or discomfort occurs.

Surgical repair, while generally safe and effective, carries a long-term risks of recurrence, pain, and discomfort.

For minimally symptomatic men, the usual basis for recommending surgery is prevention of incarceration and strangulation. These are rare events.

Is deferring surgical repair a safe and acceptable option for men with minimally symptomatic inguinal hernias?

This study entered 724 men with inguinal hernias. (mean age = 57.) All were asymptomatic or had minimal symptoms. (No discomfort which limited usual activity. No difficulty in reducing the hernia.)

Randomized to: 1) watchful waiting, or 2) tension-free repair surgery.

What happened to the surgery group? 1) Intraoperative complications in 3 patients: wound hematoma requiring return to operating room; postanesthetic hypotension; and ilioinguinal nerve injury. 2) Postoperative complications in 22%: hematomas; urinary tract infections; wound infections; orchitis; urinary retention; postoperative bradycardia; deep venous thrombosis; postoperative hypertension. 3) Overall, at 2 years, discomfort was reduced slightly, but pain limited usual activities in 2%. 4) 3% of hernias recurred. 5) More than 97% were satisfied with the treatment they received.

What happened to the watchful waiting group? 1) Pain limiting usual activities occurred in 5% 2) Cross-over to surgery 23% at 2 years, 33% at 5 years (mainly due to increased pain) 3) Complications: incarceration, bowel obstruction rare, ~ 2 in 1000 patient-years. 4) More than 97% were satisfied with the treatment they received. Overall, they experienced a slight lessening of discomfort over 2 years.

A strategy of watchful waiting (over 2 years) is a safe and acceptable option for men with minimally symptomatic inguinal hernias.

The study does not include symptomatic hernias.

Natural history studies are valuable for informing patients when they ask—What is going to happen to me?" What should I do about it? This study gives some indication of the outcomes of surgery vs WW. However, the observation period lasted a relatively short time in the life of a hernia.

Discussions between physician and patient about likely outcomes will aid negotiations between the two and enable the patient to make informed decisions. Whether to have a non-troublesome hernia repaired is an intensely personal decision. The decision will depend on many factors, two of which are 1) the duration of the hernia. 2) the age of the patient.

I believe patients whose hernias have been present for a long time and have remained non-troublesome will be more likely to avoid surgery. Recently developed hernias may cause more alarm and would lead the patient to seek a surgical consultation and tilt toward surgery.

A young man, because of his long life span, may be more accepting of surgery. He may be less willing to accept worry, bother, and anxiety over years. His hernia will be more likely to enlarge with time, and he will be more likely to develop pain and complications. (Note the study lasted only 2 to 4 years.)

An old man may be less wiling to accept surgery because his life span is shorter. He is more likely to have co-morbidity and increased risk of surgical complications.

Another important consideration: Availability of an experienced surgeon with a proven track record of fewer perioperative complications and recurrence of the hernia.

The main message of this study is to point out to middle-aged men with asymptomatic hernias that they may safely defer surgery at least for several years.

HOMOCYSTEINE

Is The Folate-Homocysteine Relationship Invalid?

4-5 HOMOCYSTEINE TRIALS:

This issue of NEJM presents two randomized trials on the effect of supplements (combined folic acid, B6, and B12) on outcomes in patients with existing atherosclerotic disease. (*Secondary prevention*) Both report no benefit, and even suggest some harm. Both were conducted in elderly patients.

An editorial in the same issue comments:

> Epidemiological studies over the past 25 years have provided ample support for the association of mild hyper-homocysteinemia with elevated risk for atherothrombosis. (*Practical pointers has abstracted several.*)
>
> But, the results of the trials cited above leads. . . "to the unequivocal conclusion that there is no clinical benefit from the use of folic acid and vitamin B12 (with or without the addition of vitamin B6) in patients with *established* vascular disease."

Is epidemiology again misleading us as it did for the putative benefit of estrogen in prevention of cardiovascular disease?

I do not think so. I am not ready to give up on the folate-homocysteine connection. I believe that limiting trials to elderly patients with established atherosclerotic disease, in an effort to reverse it, is asking too much. It may be misleading. The benefit may lie in primary prevention—ie, beginning folate supplementation at an early age to retard development of lipid accumulation and plaque formation in arteries. .

I still believe the benefit/harm-cost ratio of folate, B12, and B6 may be high. Although the benefit may be questionable (I believe this is unsettled), the harm-cost is nil, and considerably increases the ratio.

HYPERTENSION

. ***Better Estimate of Risk in the Individual***

6-1 AMBULATORY BLOOD PRESSURE MONITORING

Our knowledge about risks of hypertension and the benefits of treatment is based on taking a small number of readings with the traditional auscultatory technique in a medical setting. Such measurements have been of enormous value on a population basis, but often provide a poor estimate of risk of an individual. This may be due

in part because of poor technique of the observer, the “white coat” effect, and the inherent variability of blood pressure **(BP**).

Any clinical measurement of BP may be regarded as a surrogate measure for the “true” BP of the patient, defined as the mean level over prolonged periods.

Two techniques have been developed to improve the estimate of the “true” BP: 1) ambulatory BP monitoring (**ABPM**), and 2) home BP monitoring. Home monitoring may be used to supplant ABPM, but it is not included in most studies documenting the superiority of ABPM over traditional BP measurements.

This review considers ABPM only.

ABPM can provide: 1) the mean 24-h BP, 2) diurnal rhythm of BP, and 3) BP variability.

ABPM in other clinical conditions:

White coat hypertension

Labile BP

Resistant hypertension

Masked hypertension

Postural hypotension

Evaluating response to drugs

Predictions of clinical outcomes.

This is a concise, informative, and readable review. You may wish to read the full abstract and the original.

In my experience as a patient, determination of BP in doctor’s offices is often done improperly. There may be little opportunity to relax before the BP is taken. Usually, only one determination is made, and the observer then states “Your blood pressure is X/Y “ Accurate BP determinations are essential for the well being of all.

I believe many patients with “high blood pressure” receive drug therapy unnecessarily—mainly those with WCH. Home measurements will allow many patients to discontinue drugs.

Lifestyle interventions are essential in patients with WCH

I believe all patients with elevated BP should be monitored at home. Accurate automated machines are available of $100 or less. They provide easily repeated and reasonably accurate observations. Patients may fully relax and take several readings to obtain an average. They will help diagnosis of WCH. They will monitor response to therapy. In general practice, repeated home BP measurements are more revealing and practical than ABPM. Home BP may reduce number of doctor visits and pay for the machine.

If a machine is available at home, persons who do not have hypertension may check their BP once or twice a year. I would advise patients to avoid BP machines such as those available in pharmacies where readings may be similar to clinic readings.

ABPM should be reserved for special circumstances.

Monitors cost about $3000.

"Caution in Lowering Diastolic Pressure in Hypertensive Patients with CAD."

6-5 CAN AGGRESSIVE LOWERING BLOOD PRESSURE IN HYPERTENSIVE PATIENTS WITH CORONARY ARTERY DISEASE BE DANGEROUS?

Several reports have shown that low diastolic BP (as well as high diastolic) is associated with an increased risk in patients with coronary artery disease **(CAD**). ("J-shaped curve".) *(Ie, when diastolic becomes very low, events may be more frequent. When diastolic becomes relatively normal, events may occur less frequently. When diastolic becomes high, events may again increase in frequency.)*

This relationship would apply especially to diastolic BP since the heart, in contrast to other organs, is perfused mainly during diastole. If the J-shaped curve does exist, it should be most evident in patients with limited coronary perfusion.

This was secondary analysis of over 22 000 patients enrolled in the International Verapamil -Trandolapril Study (INVEST). All patients (mean age 66) had hypertension and CAD. All were clinically stable. All received either verapamil (*Generic*; a calcium blocker**)** or an atenolol (a generic beta-blocker) based strategy.

Diastolic BP:

Lower diastolic pressure (60 and under) led to an almost double to triple risk of primary outcomes.

The diastolic related to the least risk was between 70 and 90.

Those with diastolic of 70 and under made up only 1% of the cohort, but accounted for 20% of the primary outcome events.

Primary outcomes occurred in over 30% in those with diastolic 60 and under, and in about 35% of those with diastolic over 110. (Ie, risk increased as diastolic fell below 70, and rose as it increased above 90.)

Stroke incidence was not related to low diastolic.

For systolic pressure the J-shaped curve was much shallower.

The hazard ratios for the primary outcome showed a nadir (least risk) of 119/84.

Because perfusion occurs mostly during diastole, physiological features of myocardial perfusion are unique, and directly related to diastolic pressure. An inappropriately low diastolic pressure beyond a certain critical level could compromise myocardial perfusion.

A rapid pulse rate shortens diastolic time and perfusion. A slower pulse rate increases diastolic time and perfusion. Would not slowing the pulse rate be an additional indication for use of beta-blockers in some patients with CAD?

INSULIN

"First New Insulin Delivery System since The Discovery Of Insulin In The 1920s". But use with reservations.

2-3 INHALED INSULIN APPROVED IN EUROPE AND UNITED STATES

An inhaled form of human insulin (*Exubera*) has been approved for treatment of both type 1 and type 2 diabetes.

This brief comment lists some cautions. It is contraindicated in smokers. It is not recommended for patients with asthma, bronchitis and emphysema. It has been associated with increases in cough, dyspnea, sinusitis, and pharyngitis. And is also associated with a small mean decrease in FEV1.

There are concerns about erratic absorption. It may fail to control postprandial glucose as well as subcutaneous insulin.

It may be especially indicated for patients “who absolutely refuse to take shots”.

I believe primary care clinicians should wait for a year or two of observation of use in the general population before prescribing it.

“When Added To Oral Agents, It May Obviate The Need For Insulin Injections Entirely”.

5-5 INHALED INSULIN

In January 2006. the FDA approved the first inhaled insulin for treatment of both type 1 and type 2 diabetes (**DM-1** and **DM-2**).

For DM-1, inhaled insulin is likely to be accepted by both the public and the medical community. “It is perhaps surprising how frequently individuals with longstanding type 1 diabetes, who have adapted to multiple daily injections, are excited by the potential of needing only a single, long-acting insulin injection daily, with inhaled insulin replacing pre-meal injections.

For DM-2, the market for inhaled insulin is more complex. Newer, oral agents are under development. Insulin, regardless of route of administration, is the most potent glucose-lowering therapy. It has been used for 80 years. Its side effects are well known. Inhaled insulin has the potential to be beneficial in the long run.

Expense may be a problem for many.

This editorial lists 12 clinical points Read the full abstract

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The editorialist seems to be enthusiastic. Among patients for whom cost is no problem, I believe many will welcome and use inhaled insulin. Worldwide, for the great majority of patients with diabetes, cost will prohibit use.

MAGNET THERAPY

No Proved Benefits

1-12 MAGNET THERAPY

Magnetic bracelets, insoles, wrist and knee bands are claimed to be therapeutic. They have been advertised to cure a vast array of ills, particularly pain. A Google search yielded over 20 000 pages, most of which tout healing properties.

Many “controlled” experiments are suspect because it is difficult to blind subjects.

Published research, both theoretical and experimental, is weighted heavily against any therapeutic benefit.

“Patients should be advised that magnet therapy has no proved benefits.” If they insist on using a magnetic device, they could be advised to buy the cheapest. This will at least alleviate the pain in their wallet.”

The powerful placebo effect undoubtedly influences patients' perception of benefit.

How should primary care clinicians advise magnet-use for their patients? I believe it depends on the circumstances:

1) If patients ask beforehand if magnets provide any benefit, they can be advised that there is no scientific evidence that they benefit. Then let the patients decide.

2) If patients are already using magnets and claim they receive benefit, I would be reluctant to dissuade them. I would let the placebo effect lie unrestrained. There is no associated harm.

MAMMOGRAPHY

No Increase In Risk of BC. An Increase in Need for Repeat Mammography

4-9 EFFECTS OF CONJUGATED EQUINE ESTROGENS ON BREAST CANCER AND MAMMOGRAPHY SCREENING IN POSTMENOPAUSAL WOMEN WITH HYSTERECTOMY

Epidemiologic studies have suggested an increased risk of breast cancer **(BC)** in women receiving estrogen.

This trial compared incidence of BC in hysterectomized women who received estrogen-alone vs placebo

The Women's Health Initiative **(WHI)** enrolled over 10 500 postmenopausal women (age range 50-79; majority over age 60). All had a prior hysterectomy. Randomized to: 1) 0.625 mg combined equine estrogen (**CEE**; *Premarin*) or 2) placebo. Follow-up = 7 years.

After a mean of 7-years, the hazard ratio of invasive BC in women receiving estrogen-alone was 0.80 compared with those receiving placebo. [95% confidence interval = 0.62 to 1.04—not quite statistically significant.]

	CEE (n = 5310)	Placebo (n = 5429)	Absolute difference	NNT (7y)
Invasive BC	104 (2.0%)	133 (2.5%)	0.5%	200
Ductal carcinoma	61 (1.1%)	88 (1.6%)	0.5%	200

The number of women recalled for repeat mammography was higher in the CEE group. At one year, 9% had mammograms with abnormalities which required follow-up vs 5.5% in the placebo group. Absolute difference = 4.5%. (NNT = 22) This pattern continued throughout 7 years (36% vs 28%) Absolute difference = 8%. (NNT = 15)

In this trial, incidence of invasive BC did not differ significantly (statistically) between women receiving CEE vs placebo over 7 years. "This outcome was surprising considering prior evidence that CEE increased risk of BC."

The major consideration–estrogen-alone does <u>not</u> increase risk of BC.

The evolution of hormone replacement therapy for menopausal symptoms is fascinating.

I believe that primary care clinicians can now inform symptomatic post-menopausal women:

A. Combined E + P does slightly increase risk of CHD, stroke, BC, and thromboembolism. Women at risk may wish to avoid E+P treatment (although there is no good alternative to estrogen). Alternatively, women at increased risk may wish to accept preventive therapy to reduce risk. And to take low doses for limited duration.

B. Estrogen-alone does not increase risk of BC. It may slightly increase risk of stroke and thromboembolism. Again, they may wish to accept preventive therapy to reduce risks, and take low doses of estrogen for limited periods.

MELATONIN

Is Melatonin Ineffective?

2-7 EFFICACY AND SAFETY OF EXOGENOUS MELATONIN FOR SECONDARY SLEEP DISORDERS AND SLEEP DISORDERS ACCOMPANYING SLEEP RESTRICTION

Melatonin is classified as a "dietary supplement"[1]. It is available without a prescription.

This systematic review assessed efficacy and safety of melatonin for managing secondary sleep disorders and sleep restriction.

A. Secondary sleep disorders:

Sleep onset latency (amount of time between lying down to sleep and onset of sleep): Six trials (97 participants) showed no evidence that melatonin had an effect on sleep onset latency. The combined estimate favored melatonin by a mean of 13 minutes. However, the confidence interval = -27 to 0.9 minutes, and thus did not quite reach the 0.05 significance level. Heterogeneity between studies was substantial. When one outlier which favored placebo was eliminated, the result became statistically significant (CI = -26 min to – 8 min)

Other efficacy outcomes: Six trials showed a significant effect favoring melatonin. (Weighted mean difference = 1.9%; confidence interval = 0.5 to 3.3) "However, the effect seems not to be clinically important."[2]

B. Sleep restriction:

Sleep onset latency: Nine trial produced a combined estimate that favored melatonin, but was not statistically significant. Mean difference = -1 minute; confidence interval = -2.7 min to 0.3 min.

Other efficacy outcomes: For sleep efficiency (time spent in bed asleep), the combined estimate from 5 trials showed no statistically significant difference between melatonin and placebo. Weighted mean difference = 0.5%; confidence interval = -0.6% to 1.6%

c. Safety over 3 months or less:

The most commonly reported adverse effects were headache, dizziness, nausea, and drowsiness. The occurrence of these outcomes did not differ between groups.

Conclusion of the meta-analysis: "There is no evidence that melatonin is effective in treating secondary sleep disorders, or sleep disorders accompanying sleep restriction such as jet lag or shift work disorder."

This is a sophisticated statistical study. I congratulate the investigators on their diligence. Is it the last word on melatonin? I think not.

1 *"Dietary supplements" are not standardized, are not pure, and may by adulterated. Although melatonin is*

classified as a "dietary supplement", it is an exception. It is a simple, defined chemical entity which may permit standardization of purity and dose. The dose may have to be established on a person-to-person basis. The various studies cited did not use a standardized form and dose of melatonin.

2 *Clinical effectiveness must be judged on the basis of response by an individual patient, not on p values, not on confidence intervals. Patients know nothing about p values. There will always be outliers from the mean response. For some subjects, melatonin was associated with shortening the time to go to sleep and lengthening the time spent asleep. Undoubtedly, there is a large placebo effect of melatonin. But, in view of its safety, if my patient judged his sleep to be improved by the melatonin, I would not dispute his observation or/NOR discourage him from taking it. If a patient who had never taken melatonin expressed a desire to try it, I would not discourage her. I would suggest she purchase it in a national drug store chain, not by mail or over the Internet. My pharmacy sells 3 mg melatonin at $13 for 240 tablets.*

A new drug for insomnia has been released by the FDA—ramelteon (Rozerem). It is a melatonin agonist, targeting two melatonin receptors in the brain. 1) MT1 receptor is thought to regulate sleepiness, and 2) MT2 receptor is thought to help the body shift between phases of day and night. It has been reported to modestly decrease the time it takes to reach persistent sleep and to modestly increase the total sleep time. It is available as 8 mg tablets.

Purity and dosage is regulated by the FDA. It is classified as a non-scheduled drug. The information provided by the company (Takeda, Japan) claims there is no risk of abuse or dependence. Withdrawal effects have not been reported.

Compared with melatonin: 1) ramelteon may have the advantage of being certified as pure and with an established dose, 2) ramelteon has the disadvantage of a shorter time of use by the general population. Some adverse effects may yet appear.

(Information gleaned from the internet via GOOGLE.)

Is Melatonin Legal Fiction?

2-8 DOES MELATONIN HELP PEOPLE SLEEP?

(This editorial comments and expands on the preceding article.)

"In North America, melatonin is a popular wonder drug which has legal status and a 'nutritional' supplement, although that is legal fiction." As a result, it is not regulated as a medicine, and is advertised and sold widely—in pharmacies, health food shops, and on the internet. Millions of people use it mostly because they believe it will help them sleep.

The Dietary Supplement Health and Education Act, passed by the US Congress (1994), prevents the FDA from monitoring the quality and safety of "dietary supplements" before marketing. Supplements do not have to be dietary components.

The great majority of nostrums advertised and promoted to the general public by charlatans are taken by millions and are indeed legal fiction. They are not "nutritional" and they are not "supplements". They are not

standardized. They are not pure. Many are purposely adulterated. Melatonin may be an exception. It is a simple, defined chemical entity which may permit standardization of purity and dose. The dose may have to be established on a person-to-person basis. The various studies cited in the article did not use a standardized form and dose of melatonin. Used properly, as for jet lag, melatonin should be taken at the time night begins at the place of destination.

MENINGOCOCCAL DISEASE

Look For Early Signs Of Sepsis: Leg Pains, Cold Hands and Feet (Despite Fever) , Abnormal Skin Color

2-11 CLINICAL RECOGNITION OF MENINGOCOCCAL DISEASE IN CHILDREN AND ADOLESCENTS

Meningococcal disease **(MD)** is a rapidly progressive infection of global importance. MD is initially misdiagnosed. The infection can progress from initial symptoms to death within hours. Diagnosis must be made as early as possible. The diagnosis often depends on textbook descriptions of classic features such as hemorrhagic rash, meningism, and impaired consciousness. These signs appear late in the course of the disease.

This study determined the frequency and time of onset of clinical features of MD. Questionnaire obtained data from parents and primary care records for the course of illness before hospital admission in 448 children age 16 and younger with MD. (103 were fatal.)

Calculated the number of hours from the onset of illness to the initial consultation, and to hospital admission (or to death before admission).

Most children had only non-specific symptoms in the first 4 to 6 hours, but were close to death by 24 hours.

Three quarters of children had early symptoms of sepsis.

In all age groups, the first *specific* clinical features were signs of sepsis—leg pain, cold hands and feet, and/or abnormal skin color (pallor or mottling). Most of these symptoms appeared at a median time of 8 hours—before the first medical contact. This was much earlier than the median time to hospital admission (19 hours).

Classical symptoms of rash, meningism, and impaired consciousness appeared late. (median onset = 13 to 22 hours).

"We believe our evidence is sufficiently robust to argue that we need a diagnostic paradigm shift."

The article reported that 50% of children were referred to the hospital at the first consultation. These clinicians were sharp!

Primary care physicians in the UK have been encouraged to carry penicillin in their bags, and to administer it immediately and empirically to children who appear very ill as efforts to admit to the hospital are begun. The benefit/harm-cost ratio of this approach may be high. It may be life-saving.

I would add another non-specific early sign—does the child appear very ill?

In a career, an individual primary care clinician may never encounter a patient with MD early enough to suspect and act on the possibility of MD. If the occasion arises, recognition may be life-saving.

MENOPAUSE

"Are They Effective? Are They Safe?"

5-11 ALTERNATIVES TO ESTROGEN FOR TREATMENT OF HOT FLASHES

Hormone replacement therapy (**HRT**) is the most effective treatment. Given the efficacy of estrogen, are other treatments needed?

Caution about HRT has been raised because the large Women's Health Initiative **(WHI)** reported that, among generally healthy women, estrogen-alone increases risk of venous thromboembolism, and stroke; and combined estrogen + progestin increases risk of thromboembolism, stroke, coronary events, and breast cancer. The absolute increase in risk is small—less than 1 in 1000 women per year. Nevertheless, some women would prefer safe alternative treatment even if it is not as effective as estrogen.

A rigorous systematic review in this issue of JAMA compared non-hormonal therapies with placebo for effect on frequency of hot flashes. The review included antidepressants and other drugs; isoflavones and other plant extracts. There was considerable heterogeneity between trials. Duration of treatment in studies of these drugs was for only a few months. Long-term large trials (as the WHI) are lacking.

The review concluded that Paroxitine (*Paxil*—a SSRI; a selective serotonin reuptake inhibitor), gabapentin (*Neurontin*—an anticonvulsant and analgesic for neuropathic pain), and clonidine (*Catapres*—an antihypertension drug which stimulates CNS alpha-adrenergic receptors) may be modestly effective for relief of hot flashes.

Adverse effects include dry mouth, drowsiness, somnolence, dizziness, headache, nausea, insomnia, anxiety, and sexual adverse effects.

There is a large placebo effect from various therapies for menopausal symptoms. If a woman observes a benefit from a non-hormonal therapy, and if she experiences no adverse effects, I would not dissuade her from taking it. I would caution that long-term adverse effects are not known. They may be greater than long-term adverse effects of HRT.

I believe most "highly symptomatic" women would be willing to accept HRT if they understood that the risks of taking it are very small. And that risks of adverse effects are smaller still in younger women and in those who have few other risk factors for cardiovascular disease.

If women wish to try alternatives, they should use them for only a short term and in low dose, as with HRT.

METABOLIC SYNDROME

The Population Impact Of The MetS Is Much Greater.

1-9 METABOLIC SYNDROME COMPARED WITH TYPE 2 DIABETES AS A RISK FACTOR FOR STROKE. *The Framingham Offspring Study*

This study compared the risk of stroke in patients with DM2-alone, and with MetS-alone. Estimated the population-attributable risk of stroke associated with each.

Over 10 years, the relative risk (RR) of stroke of persons with MetS-alone (compared to those without either DM2 or the MetS) = 2.10. The RR of stroke in persons with DM2-alone was 2.5.

The prevalence of the MetS-alone in the general population was much greater than prevalence of DM2-alone.

Consequently, the population-attributable risk of stroke associated with the MetS-alone was larger than the risk of stroke associated with DM2. This was despite the higher RR of stroke associated with DM2-alone

Hyperinsulinemia and insulin resistance are accepted as prominent features of MetS. This suggests that, like impaired glucose tolerance and impaired fasting glucose, MetS may signal a prediabetic state. In the Framingham Heart Study cohort, those with MetS had a 5-fold risk of developing diabetes.

Because MetS is much more prevalent than diabetes, the population impact of the syndrome is greater.

There is a great potential for substantial reductions in stroke risk in people with MetS by treatment of its components.

MetS-alone per 100 000 population	*Risk of stroke over 10 years*	*Absolute number experiencing stroke*
22% X 100 000 = 22 000	*37/461 = 0.08 or 8%*	*22 000 X 0.08 = 1765*

DM2 per 100 000 population	*Risk of stroke over 14 years*	*Absolute number experiencing stroke*
5% X 100 000 = 5000	*12/99 = 0.121 or 12.1%*	*5000 X 0.121 = 606*

Thus, stroke occurred more than 3 times as frequently in persons with MetS-alone as with DM2-alone.

One in four adult Americans has MetS. This is a national disgrace. And a massive Public Health problem. Primary care clinicians bear a great responsibility for guiding patients for prevention, and for treatment once it is established. Clinicians should take the lead by preventing themselves from developing MetS.

Practical Pointers has reported many studies regarding the MetS. To refresh memory, the diagnosis requires 3 of 5 criteria to be present:

1) Elevated fasting Blood glucose -- 100-125 mg/dL

2) BP 130/85 or over, or treatment with antihypertension medication

3) Triglycerides 150 and over

4) HDL-c < 40 in men and < 50 in women

5) Waist circumference > 88 cm in women and > 102 cm in men.

Not all 5 criteria carry equal weight in their association with risk. It is becoming more evident that abdominal obesity may be the greatest culprit. It may carry the greatest potential for development of insulin resistance and hyperinsulinemia.

MIGRAINE

"The 'Femaleness" Of The Migraine Condition Is Inescapable." Triptans Appear To Be Useful In Prevention

4-3 THE INFLUENCE OF ESTROGEN ON MIGRAINE: A Systematic Review

Migraine attacks at or about the time of menses affects about 50% to 60% of female migraineurs.

The International Headache Society defines *menstrual migraine* as 1) migraine attacks, *without aura,* occurring *exclusively* at the time of menses (day -2; day -1; day 1; day +2 and day +3).

In some women, attacks occur, not only at the time of menses, but, in addition, at other times in the cycle. This is termed "*menstrually-related migraine*" Some attacks may be preceded by aura.

A sudden drop in plasma concentrations of estrogens may precipitate attacks. Estradiol levels are high just before menses, and then suddenly drop. In pregnancy, estrogen levels increase throughout each trimester, and sharply decline postpartum. In one study, 80% of women with migraine without aura reported no attacks in the third trimester. Nearly all reported return of migraine after delivery.

Compared with other migraines, menstrual migraine is usually more resistant to treatment, of longer duration, and associated with more functional disability.

Treatment:

1) Estrogen: "If estrogen withdrawal precipitates a migraine attack, estrogen supplementation should prevent migraine attacks." Some small studies have reported benefit. Results of studies, however, are conflicting. The level of evidence is poor.

2) Triptans: While the level of evidence from clinical trials is poor for estrogen, clinical trials using 5-HT receptor agonists for menstrual migraine have been more robust. With the understanding that menstrual migraine attacks are often predictable, short-term *preventive* administration may be helpful. One trial used sumatriptan (*Imitrex* 25 mg 3 times daily) beginning 2 to 3 days before expected migraine onset and continued for 5 days resulted in complete relief in about 50% of treated cycles and reduction in severity in others.

3) Alternative treatments: The article presents a treatment algorithm which contains approaches other than triptans for migraine in women:

A. For acute attacks: simple analgesics (acetaminophen and NSAIDS); rescue therapy with corticosteroids or opiates,

B. Daily preventive therapy: Anticonvulsants; beta-blockers; tricyclic antidepressants; calcium channel blockers.

Epidemiological, pathophysiological, and clinical evidence link estrogen to migraine. The evidence for estrogen as a preventive therapy for menstrual migraine is inconsistent. Triptans appear to be useful in prevention of the headache as well as therapy for acute attacks.

For women who experience a consistent relationship between headaches and menses, prophylactic therapy with triptans may be especially helpful and welcome.

MYOCARDIAL INFARCTION

Reduced Deaths and Reinfarction without Increase in Bleeding A New Era in Anticoagulation?

4-8 EFFECTS OF FONDAPARINUX ON MORTALITY AND REINFARCTION IN PATIENTS WITH ACUTE ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION: The Oasis-6 Randomized Trial

Despite many therapeutic advances, mortality in patients with acute ST-elevation myocardial infarction (**STEMI)** remains high. Antiplatelet therapy, thrombolysis, and angiotensin-converting enzyme inhibition improve prognosis. Primary percutaneous coronary intervention (**PCI**) offers benefits over thrombolytic therapy, but access to this procedure is limited.

Trials of unfractionated heparin, direct thrombin inhibitors, and enoxaparin (a low-molecular-weight heparin) have thus far failed to demonstrate mortality reductions. Reviparin (also a low-molecular–weight heparin) has

been shown to reduce mortality and reinfarction, but bleeding is increased when it and other agents are used with aspirin and thrombolytic therapy.

This large randomized trial evaluated the effect of fondaparinux (*Arixtra*; a synthetic pentasaccharide which rapidly inhibits factor Xa) when initiated early and given up to 8 days.

One group of patients received a fixed dose of fondaparinux (2.5 mg subcutaneously daily for 8 days) or placebo; another group received fondaparinux or 2 days of unfractionated heparin + placebo.

Overall, at 30 days and at 3 to 6 months, death and reinfarction occurred less frequently in the fondaparinux group. (NNT = 66 and 70).

Benefits were evident in those receiving no reperfusion therapy and in those receiving thrombolysis. No benefit in those undergoing PCI.

Severe bleeding was less likely in the fondaparinux group. (Overall, 1.0% vs 1.3%)

"Unlike other antithrombotic agents, such as low-molecular-weight heparin, direct thrombin inhibitors, or intravenous antiplatelet agents, fondaparinux reduced death and reinfarction without increasing bleeding or hemorrhagic stroke."

"Addition of fondaparinux to thrombolytic therapy probably represents an attractive, effective, and safe option as an initial adjunctive antithrombotic agent in STEMI in patients not undergoing primary PCI."

I wondered if the name of the drug (ending in X) was related to its effect of factor X. Note also the X in Arixtra.

The standard dose and the reduced risk of bleeding are notable benefits.

See also "Comparison of Fondaparinux and Enoxaparin in Acute Coronary Syndromes" (OASIS-5 NEJM April 6, 2006; 354: 1464-75) This study compared fondaparinux (2.5 mg daily) with enoxaparin (Lovenox), a low-molecular weight heparin, in over 20 000 patients with unstable angina or myocardial infarction without ST elevation. Major bleeding occurred less frequently in the fondaparinux group. At 30 days, and long-term, mortality and morbidity favored fondaparinux.

Fondaparinux has been reported to be more effective than enoxaparin in preventing venous thromboembolism. (See Practical Pointers February 2006.)

An editorial, first author Raymond J Gibbon (NEJM April 6, 2006; 354; 1524-27) suggests that 2 specific activities of fondaparinux may be responsible for the reduced risk of bleeding: 1) inhibition of factor Xa within the clot, and 2) lack of inhibition of platelet function.

NONSTEROIDAL ANTI INFLAMMATORY DRUGS (NSAIDS)

All, Except Possibly Naproxen, Carry Some Risk of Atherothrombosis.

6-2 DO SELECTIVE CYCLO-OXYGENASE-2 INHIBITORS AND TRADITIONAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS INCREASE THE RISK OF ATHEROTHROMBOSIS?

A Meta-analysis of Randomised Trials

. This meta-analysis included 138 randomized trials comparing selective COX-2 inhibitors versus 1) placebo,

and 2) traditional non-selective NSAIDs. All studies included information about serious vascular complications (myocardial infarction [**MI**], stroke, and vascular death).

Selective COX-2 inhibitors vs placebo:

An increased risk associated with the former (1.2% per year vs 0.9% per year) [Absolute difference = 0.3%; NNT to harm one patient over 1 year = 333.]. This was chiefly attributed to an increase in risk of MI (0.6 per year vs 0.3 per year) with little apparent difference in other vascular outcomes.

"There was no significant heterogeneity among the different selective COX-2 inhibitors."

Traditional NSAIDs versus placebo:

	Rate ratio for vascular events
Naproxen vs placebo	0.92 (Ie, less risk than placebo)
Ibuprofen vs placebo	1.5
Diclofenac vs placebo	1.6

Selective COX-2 inhibitors vs traditional NSAIDs:

Overall, there was no significant difference in incidence of serious vascular events between 1) selective COX-2 inhibitors and 2) traditional NSAIDs—340 vascular events during over 33 000 person years of exposure to 1), and 211 vascular events in over 22 000 person-years of exposure to 2). [1% per person-years vs 0.9% per person-years.

Selective COX-2 inhibitors were associated with a 1.4-fold increased risk of serious vascular events largely due to a two-fold increase in myocardial infarction.

High doses of ibuprofen and diclofenac were associated with a similar increased risk.

High doses of naproxen were *not* associated with increased risk.

Traditional NSAIDs also inhibit the enzyme COX-2. If selective COX-2 inhibitors are associated with increased risk, it would seem reasonable to assume that traditional NSAIDs would also increase risk.

Do patients with higher baseline risks of MI have higher risk of MI associated with COX-2 inhibitors? If so, would not reduction of other risk factors (smoking, dyslipidemia, hypertension) reduce the risk of MI associated with COX-2 inhibitors and higher-risk traditional NSAIDs? Would it be more dangerous to prescribe NSAIDS to these patients?

All NSAIDs except naproxen (Generic; Naprosin) carry risk of atherothrombotic disease, especially when used for long periods at high doses. We should not forget that NSAIDs have adverse effects on the kidney, blood pressure and heart (increasing risk of congestive failure).

I believe the widespread acceptance and use of COX-2 inhibitors is a tribute to the marketing skills of drug companies.

"Patients Should Always Be Offered Acetaminophen Before Resorting To Other Analgesics."

6-3 LIFE WITHOUT COX-2 INHIBITORS ***Doctors Need To Broaden Their Approach To Pain In Older Patients***

Several selective COX-2 inhibitors have been withdrawn from the market. Use of others is being limited because of increased risk of myocardial infarction in long-term users.

"Have we lost a truly superior option? Probably not. Other pharmacological and non-drug options may be reasonably effective, equally safe, and less costly."

Acetaminophen (eg, *Tylenol*) offers effective and safe treatment for general musculoskeletal pain, including osteoarthritis. "Patients should always be offered acetaminophen at sustained doses before resorting to other analgesics." It has a relatively high safety margin except in overdose. It should be limited to 4 g daily, and less if the patient has liver disease or has high alcohol intake.

Opioids can be used as a last pharmacological resort. "Concerns about addiction are largely unfounded." Dependence—withdrawal symptoms if drugs are withdrawn—can be expected. "Fear of dependency and addiction is not sufficient justification to fail to relieve pain."

The editorialists comment on other pain-relieving measures: topical diclofenac; braces; exercise; glucosamine.

"Rather than lamenting the loss of COX-2 inhibitors—an intervention more popular than proved—we will best serve our patients by thinking creatively about other approaches to their pain." Presenting a menu of possible treatments and working with patients to choose those that best suit their lifestyle and health beliefs is the optimal way to find solutions to their chronic pain.

Some drugs are available combined with acetaminophen. Many variations are available allowing for personal choice. None offers complete relief. All have some degree of placebo effect.

I believe most older people with osteoarthritis pain accept, and live with some degree of discomfort. Many go on to consider joint injections and replacement therapy.

OBESITY

Proposing That Fat Accumulations In The Myocardium Are Toxic.

4-12 ADIPOSITY OF THE HEART, REVISITED: A Narrative Review

Under healthy conditions, most triglyceride is stored in adipocytes. The amount of triglyceride stored in non-adiposite tissues (pancreas, liver, and myocardium) is minimal and tightly regulated. When this regulation is disrupted, triglycerides may accumulate excessively in these organs (steatosis). The accumulation may culminate in irreversible cell death (lipotoxicity) and lead to several clinical syndromes: non-alcoholic hepatic steatosis; pancreatic B-cell failure; and dilated cardiomyopathy

Investigations are now revisiting the hypothesis that excessive deposits of lipids within myocardial tissue (that is, cardiac lipotoxicity) is an important, but forgotten, cause of non-ischemic dilated cardiomyopathy. Imaging techniques now permit precise and reproducible quantification of intra-cellular triglyceride in various human

organs, including the myocardium. This presents a novel mechanism that may act independently of coronary artery disease to cause dilated cardiomyopathy.

"Myocardial lipid content may be a biomarker and a putative therapeutic target for cardiac disease in obese patients."

However. . . "A direct association between myocardial lipid content and left ventricular performance has yet to be reported."

This, of course, is not a practical point at this time. I could not resist abstracting it. Indeed, I am old enough to remember when the concept of the fatty heart was taught in medical school.

This makes sense. If fat can accumulate in the liver, why not in the myocardium?

Watch for further developments.

"Later Adolescence Is A Life Stage With Unique Associations Between Poverty And Overweight."

5-10 TRENDS IN THE ASSOCIATION OF POVERTY WITH OVERWEIGHT AMONG ADOLESCENTS 1971-2004

Does socioeconomic status (eg, poverty) affect prevalence of overweight?

The US National Health and Nutritional Examination Surveys (NHANES) conducted four surveys between 1971-2004, and examined trends in prevalence of overweight among adolescents ages 12 to 14 and 15-17.

For a family of 4, the US Census Bureau's poverty threshold in 2004 was $19,157. In the 4 surveys, the percentage of adolescents living in poverty ranged from 16% to 22%.

Prevalence of overweight in NHANES 1999-2004 age 15 to 17:

	Not poor	Poor
Overall	14%	23%
Non-Hispanic white	12%	21%
Non-Hispanic black	22%	25%

Later adolescence is a life stage with unique associations between poverty and overweight. Food choices and physical activity in adolescence differ considerably from those in early childhood and adulthood.

Among 15 to 17 year-olds, trends in overweight showed a greater impact among families living below the poverty line. Increased consumption of sweetened beverages, physical inactivity, and breakfast-skipping may contribute to the difference.

What to do about it? I doubt much can be done about the obesity problem in the near future. It is an extremely complex, multifaceted socio-economic problem, not merely a heath problem. It will take a sea change.

I abstracted this article mainly to express my belief that primary care clinicians should have, and express, compassion and understanding of the problems of those living in poverty. They do indeed live in more dangerous and unattractive neighborhoods. This reduces opportunities for physical activity. They cannot afford the SPA.

They may have less understanding about nutrition. They do not have the funds to purchase healthy foods. They may accept the perceived instantaneous pleasure of high fat, high calorie foods. It is not fair to tell a poor overweight person that "It is all your fault. You should do better"

As one article I previously abstracted commented—advising the poor to eat healthy and get more exercise does not lead them to eat mangos and play tennis.

"At 12 Months, Only 25% Of The Original Sample Were Still Keeping Their Allocated Diets"

6-7 RANDOMIZED TRIAL OF FOUR COMMERCIAL WEIGHT LOSS PROGRAMS IN THE UK

The BBC "Diet Trials"

"Most adults in the United States diet at some time." Long-term success rates are poor.

This randomized unblinded trial considered 4 diets available in the UK vs a control group:

A. Dr Atkins' new diet revolution (a self-monitored low carbohydrate diet.)

B. Weight Watchers (an energy controlled diet with weekly group meetings.)

C. Slim-Fast (a meal replacement approach.)

D. Rosemary Conley's eat yourself slim diet and fitness plan (a low fat diet and a weekly group exercise class.)

All 4 diets resulted in about an equal weight loss over 6 months: (Intention-to-treat basis)

	Atkins	WW	Slim-Fast	Rosemary	Controls
Loss (kg)	6	7	5	6	Gain of 0.6 kg

People who kept their allocated diet lost about 10% of their weight despite some weight rebound. "These results provide information about the 'best effect' that the most highly motivated subjects may hope to achieve over one year. "

Would adopting a revolving diet plan (ie, switching from one to another after a month) benefit some people?

The only proven remedy for obesity is bariatric surgery.

OSTEOPOROSIS

Is this the final word on calcium + vitamin D supplementation to reduce risk of fracture ?

2-4 CALCIUM PLUS VITAMIN D SUPPLEMENTATION AND RISK OF FRACTURES IN OLDER WOMEN

This trial tested the hypothesis that calcium + vitamin D **(C + D)** supplementation, begun at an advanced age in women, would lower risk of hip fractures and other fractures as compared with placebo.

The Women's Health Initiative recruited over 36 000 postmenopausal women age 50 to 79 (mean age = 62 at baseline). All were living in the community and were considered healthy.

Randomized to: 1) 1000 mg calcium + 400 IU vitamin D daily, or 2) placebo.

Bone mineral density was greater in the calcium + vitamin D group at year 7 by 1%.

Fracture rate overall*	Ca + D	Placebo
Hip	175	199

Vertebral	181	197
Forearm of wrist	565	557
Total	2102	2158

(*Intention-to-treat. No statistical difference between groups.)

Among women who were adherent (ie, took at least 80% of their study medication), C + D supplementation resulted in a 29% reduction in hip fracture—68 in the C + D group vs 99 in the placebo group (95% confidence interval = 0.52-0.97—statistically significant).

"The trial demonstrated that calcium with vitamin D supplementation diminishes bone loss at the hip, but the observed 12 percent reduction in the incidence of hip fracture (the primary outcome) was not statistically significant." "It is plausible that there was a benefit only among women who adhere to the study treatment." Only 59% of women were still taking the intended dose of the study medication at the end of the trial.

Although the statistically null primary effect argues against recommending universal calcium with vitamin D supplementation, the findings provided evidence of a positive effect of calcium with vitamin D on bone health in older postmenopausal women

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I would amend the conclusion to state that calcium and vitamin D supplementation did not significantly reduce hip fracture when begun at age 62. I would not expect much reduction in fractures in women when C + D supplementation is begun long after the menopause. Intakes of C and D are almost universally deficient in the USA at all ages. Efforts to develop and maintain healthy bone structure are a life-time endeavor. Primary care clinicians should ensure their patients achieve adequate intakes beginning in childhood.

The benefit/harm-cost of C + D supplementation is, I believe, very high. Entering menopause with healthy bones will reduce hip fractures and alleviate the frequency of disabling kyphosis which plagues many older women.

PALLIATIVE CARE

Adequate and Timely Communication with Patients Is One of the Great Lacks of the Medical Profession

6-14 THE PATIENT'S JOURNEY: PALLIATIVE CARE—A PARENT'S VIEW

This is an account of the pain a family endured during the painful illness and death of a son. Read the full abstract and the original article.

A mother, Stephanie, recounts the emotional struggle she, her family, and her 17-year old son Andrew endured during his extensive treatment and death from a brain tumor. They were finally told that the end was near. "Although the progress of the illness—the months of anxiety, hospital admissions, treatments, improvements, relapses—does to a certain extent prepare you for such news, it is difficult to describe the effect of it. I think crushing, stunning defeat after a prolonged painful struggle sums it up. And, of course, it is the end of all hopes for recovery when treatment stops and palliative care takes over."

So what did the experience of the son's last weeks show the mother?

It would have been good to have someone in overall charge of palliative care.

It would have been useful to discuss all possible options and contingencies for palliation.

The philosophy of acceptance is not enough for siblings. Attempts to prepare the sisters were insufficient. Preparation should have been started earlier with professional help.

Despite the excellent medical care and loving nursing the cancer unit offered, dying in such a unit is not the best choice if one has a choice.

Palliative care in the community offers an extra option for the last weeks of a child's life. This is especially beneficial to families with terminally ill children, enabling the child to remain at home in familiar surroundings and with the people who love them most.

I sensed that the family, at last, did achieve a degree of peace.

Church and clergy were not mentioned. Hospice was not mentioned. Those of us who have suffered the loss of a loved one with the help of church and Hospice care know how supportive and reassuring they are.

I wonder why greater pain relief could not have been accomplished at home. I believe most families can be taught to administer morphine safely.

Communication1 Communication! Communication! Adequate and timely communication with patients is one of the great lacks of the medical profession. The family did not have access to a specific person (eg, a primary care clinician) who knew the situation and could act immediately to counsel and support. Their support was fragmented.

PATIENT AGENDA FORM

5-1 EFFECT OF PATIENT COMPLETED AGENDA FORMS AND DOCTORS' EDUCATION ABOUT THE AGENDA ON THE OUTCOME OF CONSULTATIONS

"Although identification of why the patient has attended is a key objective of the consultation, doctors commonly fail to achieve this."

Enhancing patients' ability to participate in the consultation improves communication between patient and doctor.

This study used an agenda form in which patients write down the reason for the consultation, and what they expect from it. The form is completed just before the consultation, and then presented to the doctor.

Randomized, controlled trial entered and followed 45 general practitioners and 857 patients. Half of the patients were randomized to the agenda form; half to no agenda forms (controls).

Results:

	No agenda form	Agenda form
Duration of consultation (min)	7.1	8.0
No. of problems identified	1.7	1.9
Time per problem (sec)	306	295

When patients made their own agenda explicit in the consultation:

A. Doctors identified more problems.

B. Consultations lasted longer. (Due to more problems identified.)

C. Patients were more satisfied with the depth of the consultation.

Neither intervention decreased the number of “By the way, doctor” presentations.

For each consultation session of 18 patients (*I presume an estimated day’s work*), the combined interventions identified an additional 9 problems, and sessions were 34 minutes longer.

Although this increased doctor’s workload, it represents a pool of unrecognized need among patients.

The agenda form printed on a single page:

To help your doctor:

1. Please make a list of the points you want to raise.

2, Do you have any thoughts about these points? (For example, the cause of your problem)

3. Do you have any questions?

4. What would you like the doctor to do? (please circle yes or no)

A. Prescribe	*Yes*	*No*
B. Explain	*Yes*	*No*
C. Investigate	*Yes*	*No*
D. Write note	*Yes*	*No*

5. Other (please say what it is).

I believe some primary care clinicians and patients will find this approach helpful If the list of problems is long, the doctor may create an agenda and sort the problems in order of importance, and consider some of them at return visits.

I was surprised that the number of “By the way, doctor” presentations by patients was not decreased.

Far additional commentary on “By the way, doctor” see Practical Pointers November 2005

PERIPHERAL ARTERIAL DISEASE

Clinically Significant Increase In Walking Distance

5-9 RAMIPRIL (An ACE Inhibitor) MARKEDLY IMPROVES WALKING ABILITY IN PATIENTS WITH PERIPHERAL ARTERIAL DISEASE

Randomized, double-blind placebo-controlled trial followed 40 patients (mean age 66; almost all male) with symptomatic peripheral artery disease (**PAD**). None had a history of diabetes or hypertension.

Forty two % were smokers. Many had hypertension. In some, LDL-cholesterol levels exceeded 100 mg/dL. Only 27% were on lipid-lowering therapy.

Asked participants to refrain from exercise, smoking, and caffeine for 24 hours before testing.

Randomized to: 1) ramipril 10 mg daily, or 2) placebo for 24 weeks.

Measured pain-free and maximum walking time during a standard treadmill test.

Completed a Walking Impairment Questionnaire. (**WIQ**)

Treadmill test

At baseline:	Placebo	Ramipril
Median pain-free walking time (s)	168	160
Maximum walking time (s)	244	234

At 24 weeks

Median pain-free walking time (s)		387
Maximum walking time (s)	234	685

The WIQ in the ramipril group indicated improvement in scores of walking distance, speed, and stair climbing. The increase in walking distance (calculated as a mean of 400 meters in the ramipril group) is clinically significant and would appreciably affect daily functional capacity. The improvements in the WIQ scores were consistent with the measured improvements, demonstrating that ACE improves the ability to perform daily activities.

I do not know why the trial excluded patients with diabetes and hypertension.

Note that the trial was drug vs no-drug. It did not address risk factors which primary care clinicians would treat in addition to drug therapy. Smoking cessation was not stressed. (Subjects were asked to stop smoking for 24 hours before testing). Dyslipidemia was not aggressively treated. Outcomes may have differed if these risks had been treated, and ACE therapy may not have resulted in as great an improvement.

I would be willing to add an ACE as a therapeutic trial in these patients.

PHARYNGITIS

Centor Score + Rapid Streptococcal Antigen Test

3-4 MANAGEMENT OF ACUTE PHARYNGITIS IN ADULTS

Viruses are the main cause of acute pharyngitis in adults. “Only about 10% of incidences are bacterial, mainly caused by group A beta-hemolytic streptococci, which is the only indication for antimicrobial therapy.”

Acute group A streptococcal pharyngitis (**GASP**) is a self-limited disease with low complication rates. Antibiotic therapy should be prescribed for few patients with acute pharyngitis. Physicians prescribe antibiotics for the great majority of patients.

Penicillin V effectively reduces symptom duration by a few days, spread of the disease, and incidence of suppurative complications and rheumatic fever. (The latter is now rare in developed countries.)

The Centor score[1], based on 4 clinical findings, enables clinicians to estimate probability of GASP in adults. Recently introduced rapid streptococcal antigen tests (**RSAT**—Abbott Laboratories) using optical immunoassays give immediate results with 10% to 20% false negatives and 5% false positives.)

This prospective cohort study included 372 adult patients (mean age 30) with acute pharyngitis who presented to a primary care clinic. Most patients had moderate illness with clinical scores of 2 or 3. Patients with 0 or 1 of the clinical features were excluded. (Most experts agree that this group does not require further testing and antibiotic therapy.)

All were tested by RSAT and throat culture.

Systematic RSAT (compared with culture as the gold standard) achieved high sensitivity—91% (91% true positives; 9% false negatives], and specificity—95% (95% true negatives; 5% false positives).

The predictive value of a positive RSAT was 91/ 91+ 5 = 91/96 =95%. This resulted in-nearly optimal antibiotic treatment (37%). Antibiotic overuse and underuse were minimal (3% and 3%).

RSAT can be a valid diagnostic test particularly when combined with the Centor clinical score. The best clinical approach for diagnosis and treatment is systematic RSAT in patients with at least 2 clinical findings.

Many patients who feel acutely ill may not be happy about waiting 2 or more days for results of a throat culture before starting treatment. Communication delays might also be a problem. A single culture has less than 100% sensitivity. Culture may not be a reasonable choice for primary care.

1 *The Centor Score*

1) Temperature 38^0 C (100.4 F) or higher.

2) Tonsillar exudates

3) Tender cervical adenopathy

4) No cough or rhinitis.

PHYSICAL FITNESS PHYSICAL ACTIVITY

If You Can't Lose Weight, at Least Get in Better Physical Shape.

3-2 ASSOCIATION OF PHYSICAL ACTIVITY AND BODY MASS INDEX WITH NOVEL AND TRADITIONAL CARDIOVASCULAR BIOMARKERS IN WOMEN

More than half the US population does not meet recommended levels of physical activity, and 65% are overweight. The problem is more common in women than in men.

This study asks: Are a high BMI and low physical activity associated with adverse biomarkers for cardiovascular disease? Which of the two is most strongly associated?

Women's Health Study entered over 27 000 apparently healthy women (mean age 55 at baseline) in 1992-95. Mean BMI = 26. Median leisure physical activity = 601 kcal/wk.

Main outcome measure = association of BMI and physical activity with levels of C-reactive protein, HDL-cholesterol, LDL-cholesterol, total cholesterol, fibrinogen, and apolipoprotein A1.

Higher levels of BMI and lower levels of physical activity were independently associated with adverse levels of almost all lipid and inflammatory biomarkers.

There were stronger associations with BMI than with physical activity. Adipose tissue, particularly visceral adipose tissue, is metabolically active, promoting a thrombotic and inflammatory state as well as a atherogenic lipoprotein state.

Within each BMI category being physically active was associated with more favorable cardiovascular biomarker levels. A modest level of physical activity (about 2.5 hours weekly) was significantly associated with more favorable biomarkers, even in overweight and obese individuals.

The main message for primary care might be—If you can't lose weight, at least get in better shape physically. It would be better, however, if you lose weight and get in better shape.

It is very unlikely that an overweight or obese person will lose weight and maintain the loss with diet alone.

A combination of calorie restriction and increased physical activity is required.

Regular Physical Activity Before Pregnancy Is Associated With Lower Risk Of GDM

3-8 A PROSPECTIVE STUDY OF PREGRAVID PHYSICAL ACTIVITY AND SEDENTARY BEHAVIORS IN RELATION TO THE RISK OF GESTATIONAL DIABETES MELLITUS

Gestational diabetes mellitus **(GDM)** is among the most common complications of pregnancy. It affects about 4% to 7% of pregnancies. Recently, there has been a substantial rise in incidence, in parallel with the rise in incidence of obesity and type 2 diabetes **(DM-2).** This study assessed whether pregravid physical activity is associated with risk of GDM.

This study included over 21 500 women who reported at least one singleton pregnancy between 1990 and 1998. Periodic validated questionnaires asked participants to report the amount, type, and intensity of *pre*-gravid physical activity; and sedentary behavior.

After controlling for BMI, dietary factors, and other covariates, there was a statistically significant inverse relationship between physical activity and risk of GDM.

Relative risks **(RR)** of GDM according to quintiles (lowest vs highest) of pre-pregnancy activity scores:

	1st quintile	5th quintile
Total activity		
Women , No	4377	4344
MET-hours per wk	0.2	>40
Cases, No.	312	251
RR	1.00	0.81[1]

"In this large prospective cohort study of women, prepregnancy physical activity, in particular increasing vigorous physical activity, was associated with significantly lower risk of GDM. "Brisk or striding walking, and increased stair climbing were associated with substantially reduced risk, independent of total physical activity levels and prepregnancy BMI.

Physical activity during the year before pregnancy and during adolescence are strong predictors of physical activity during pregnancy. "It is plausible that much of the benefit we observed for pregravid physical activity also reflects continued activity during pregnancy.

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1 *Reporting results in terms of relative risks, and relative risk reductions can be clinically misleading as well as clinically meaningless. The article could just as well have reported that "Exercise reduces risk of GDM by 19%." Relative risks may indicate a statistical benefit (ie, the probability that the results of the trial are due to chance may be very small), but are not helpful clinically.*

Absolute risk reductions are much more meaningful from a clinical viewpoint. The absolute benefit of the highest quintile vs the lowest quintile of total physical activity (by my calculations based on their tables) = 1.3%. (Ie, there was between 1% and 2% benefit from exercise in reducing development of GDM. I believe this is a

clinical benefit. The benefit/harm-cost ratio may be very high, because, although the absolute benefit is small, the denominator of the ratio (harm-cost of physical fitness) is nil.

Women should be encouraged to maintain physical fitness before and during pregnancy.

PLACEBO EFFECT

Device Outperforms Pill

2-2 SHAM DEVICE VERSUS INERT PILL: *Randomized Trial Of Two Placebo Treatments*.

This trial, in patients with arm pain, investigated whether a sham acupuncture needle had a greater placebo effect than an inert pill.

Participants (n = 119) were community dwellers who had arm pain due to repetitive use that had lasted at least 3 months despite treatment. All had pain scores of 3 or more on a 10-point pain scale.

Randomized to 1) acupuncture with a sham device twice a week for 6 weeks, and 2) an inert placebo pill once daily for 8 weeks.

Pain scores and the symptom severity scale decreased significantly more in the sham group than in the pill group.(-0.33 vs -0.15; and -0.007 vs -0.05) (In the sham acupuncture group, the downward slope in the 10-point pain scale each week was significantly steeper than the downward slope in the placebo pill group.)

Differences in grip strength and arm function were not significant.

Nocebo effects were totally different in the two groups, and clearly mimicked the information given at informed consent. Sham acupuncture subjects were told that their pain might be temporarily aggravated: placebo pill subjects were told that they might experience sleepiness, dry mouth, dizziness, and restlessness. One quarter to one third of subjects reported such adverse effects. “Our findings contribute to the debate on the influence of information provided at informed consent and subsequent reported adverse effects.” “We found that reported side effects perfectly mirrored the information provided to participants.”

“Placebo effects seem to be malleable, and depend on the behaviors embedded in medical rituals.”

The same group commented in 1998 “No longer is it sufficient for a therapy to work; it must be better than placebo.”

Placebos are both fascinating and powerful. Indeed, I believe at times the placebo effect is the primary care clinician’s best friend. I would not discourage placebo use in a patient who perceives benefit—provided the placebo is not harmful and does not preclude other therapy of proven benefit.

Although we may argue about whether it is ethical to prescribe a placebo, I believe many, if not most, primary care clinicians will occasionally prescribe a drug for which they have little or no expectation of pharmacologic benefit.

To assess the power of the placebo effect, it is necessary to compare a group of patients who receive no-treatment and no-placebo, with a group receiving a placebo.

A part of the effect of all active drugs is due to the placebo effect.

The strength of the placebo depends on its form (as in this study), the enthusiasm and belief of the clinician, and the culture and belief of the patient. If 1000 patients are given a placebo, and 1) 500 enthusiastically and

conscientiously take it, and 2) 500 patients take it irregularly, without complying with the regular schedule, outcomes in group 1) will be better than in group 2).

There is no doubt that totally (pharmacologically) inactive substances can produce demonstrable effects on brain function. Inert pills and devices can have harmful (nocebo) effects.

PRIMARY CARE MEDICINE

"Much More Important Than Specialty Care In Providing Services To Those Most In Need"

3-9 STRENGTHENING PRIMARY CARE TO BOLSTER THE HEALTH CARE SAFETY NET

Medical graduates' interest in family medicine is on the decline.

"There is no evidence that more specialty care improves population health. Nations with a strong primary care infrastructure have far better health outcomes than those such as the United States that emphasize specialty medicine."

One reason for this phenomenon may be that primary care is much more important than specialty care in providing services to those most in need (ie, vulnerable populations). Primary care serves to narrow health disparities associated with ethnic group, socioeconomic, and geographic residence status. Physicians in the USA are not equitably distributed. This causes pockets of medically underserved communities, while others have an excess supply. Market forces in the US health care sector have failed to supply physicians where they are needed.

Large numbers of uninsured Americans lack access to care. Much greater attention must be given to achieving a strong and expanded primary care workforce. "Bolstering this safety net is one of the best strategies for improving the health of the nation." The cornerstone of a national strategy for strengthening the safety net begins with ensuring a well-trained cadre of primary care professionals.

I believe primary care is one of the most gratifying of medical specialties. And one of the most difficult to perform well. Young practitioners entering primary care may not expect to be rewarded financially as much as high-tech specialists, but they will have enough income to adequately care for their family, to have a comfortable and safe home, to educate their children, to enjoy an occasional relaxing vacation, and to save for retirement. All this while experiencing great self-satisfaction, and of course, working very hard.

We should not forget the exceptional contributions of Nurse Practitioners who work closely with primary care physicians. They add immeasurably to the quality and accessibility of care.

Primary care clinicians must develop an intimate connection to other health-care providers in the community and at referral centers. Timely availability of specialist consultants is essential in order to provide adequate care to primary care patients.

PROSTATE CANCER

Should PSA Screening Be Expanded Or Curtailed?

3-5 PROSTATE CANCER SCREENING

Prostate cancer **(PC)** screening with prostate specific antigen **(PSA)** is controversial.. Major professional associations offer different screening guidelines.

The American Urological Association and the American Cancer Society endorse PSA screening (and digital rectal examination). Screening is recommended to begin at age 50 for average risk men who have at least 10 years of remaining life expectancy. The PSA threshold for biopsy referral is 4.0 ng/mL.

The US Preventive Task Force recently concluded that there was insufficient evidence to recommend for or against routine screening. They encourage physicians to discuss the risks and benefits of screening with their patients to guide them to an informed screening decision.

This debate addressed 3 key issues about screening on the basis of evidence published 2000-2005.

Should screening begin before age 50?

Should screening extend beyond age 70?

Should a PSA level below 4.0 ng/ml trigger biopsy

One of the debaters (Dr. Hoffman) argues that the data support maintaining a conservative PSA screening approach. The second debater (Dr. Catalona) argues for extending the usually recommended limits of screening.

Both commentators refer to the 2005 National Comprehensive Cancer Network which recommended baseline screening at age 40 for all men of average risk who choose screening. Men with a PSA above or equal to 0.6 should then be screened annually. Those at a lower level should be retested at age 45. This algorithm is based on retrospective data from the Baltimore Longitudinal Aging Study which found that men age 40-49 with PSA above the age-range median (0.6 ng/mL) were 4 times as likely to develop PC as men with lower levels.

Prostate cancer screening has been a favored subject in the primary care literature. Practical Pointers has abstracted relevant articles in July and May 2005; May, June, July and November 2004; and April and May 2003.

The benefit/harm-cost ratio of PSA screening:

Benefit—Screening will undoubtedly spare some men development of metastatic disease and death. (This is the bait.)

Harm—Potentially unnecessary interventions; perioperative morbidity and death; surgical complications (importance and incontinence); and especially the overhanging cloud of anxiety and obsession related to long term fear of "cancer"

Cost—even with the present criteria for screening, costs to society are high. Widening the age limits for screening, and lowering the PSA level criteria for biopsy will greatly increase costs.

The benefit/harm-cost ratio of PSA screening is very low. The bloom is coming off PSA screening.

I believe primary care clinicians should never order a PSA without first informing the patient about possible harms and benefits. Including a PSA in the routine diagnostic biochemical profile as a matter of course is a serious mistake. Men who choose and insist on screening should be pre-informed.

Digital rectal examination remains a valid screen.

RADIATION HAZARD

Danger, Especially From Repeated CTs

5-12 HEALTH EFFECTS OF IONIZING RADIATION FROM DIAGNOSTIC CT

An estimated 60 million computerized tomographies (CTs) were done in the USA in 2002. This represents 70% of all medical X-ray exposure.

The National Academy of Science report on the Biological Effects of Ionizing Radiation indicated that a single population dose of 10 mSv is associated with a lifetime attributable risk of developing a solid cancer or leukemia is 1 in 1000. The typical abdominal examination dose is between 10 and 20 mSv. The breast glandular dose during a pulmonary artery CT angiogram is 20 mSv.

"The ionizing radiation exposure from a single abdominal or chest CT may be associated with elevated risk for DNA damage and cancer formation." The radiosensitive tissues are predominantly within the field of view of common chest, abdominal, and pelvic CT scans.

Many patients are exposed to multiple examinations that increase cumulative dosing. One subset of patients with renal colic had total exposure rates between 19 and 154 mSv.

Referring physicians are largely unaware of the potential harmful effects from CT radiation exposure. Radiologists doing CT examinations consider the radiation exposure of limited concern. "Many are unaware of the dose of radiation delivered to the patient." The risk may not be explained clearly to patients before obtaining consent.

Radiation effects may not manifest until 5-20 years after exposure. Causal relations are not apparent on an individual basis.

The editorialists suggest some means by which exposure can be limited, including greater use of MRI.

I do not know enough about radiation physics to comment. I hope some radiologists will respond.

I believe the caution is appropriate. I abstracted the editorial because primary care clinicians often refer patients for CT. They bear some responsibility for the cumulative doses of radiation.

Commercial entrepreneurs continue to offer unselected CT screening, including whole body screening, to the general public. Some clinicians are enthusiastic about CT screening for coronary artery calcification. I believe there is little concern about radiation exposure.

I believe the scanning procedure used depends on the equipment available in the community and the expertise of the radiologist.

ROTAVIRUS VACCINES

"The Time For A Rotavirus Vaccine May Have Finally Arrived."

1-3 THE PROMISE OF NEW ROTAVIRUS VACCINES

This issue of NEJM, reports promising results from large clinical trials of two new oral vaccines:

1) *Rotateq* (Merck) is a penta-valent vaccine based on a bovine strain that contains 5 human-bovine viruses. It is naturally attenuated for humans. The bovine virus grows less well in the human intestine, so the aggregate titer required to immunize is greater. Three oral doses are required, with at least a

month between doses. The vaccine strains are infrequently shed in the stool. It is not broadly cross-protective against other serotypes.

2) *Rotarix* (Glaxco Smith-Kline) is an attenuated, mono-valent vaccine derived from the most common human retrovirus strain. It is given in two doses one month apart.. It replicates well in the gut, and is frequently shed (like natural infections) in the stool. It cross-protects against most other serotypes.

Both vaccines demonstrate impressive efficacy against severe disease (85% to 98%) .

Both vaccines demonstrated a reassuring safety profile. There was no significant difference in the rate of intussusception between the vaccine and placebo

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This may be a giant step forward.

I do not understand the pathophysiology of the increased risk of intussusception reported in studies of the old vaccine (1999). Anyone out there who can suggest a connection?

SCABIES

"Topical Permethrin is A Reasonable First Line Therapy"

4-6 SCABIES; Review Article

The mite is an obligate parasite that completes its entire life cycle on humans. Mites cannot fly or jump. The more parasites on a person, the greater the likelihood of transmission, either direct (skin-to-skin—the predominant method) or indirect (through infested bedding, clothing or other fomites).

The diagnosis rests largely on the history and examination of the patient as well as the family and close contacts. Generalized and intense itching (worse at night) usually spares the face and head. Lesions are located mostly in the finger webs, on flexor surfaces of wrists and elbows, axillae, buttocks, genitalia, and breasts of women.

One study reported that the presence of diffuse itching and visible lesions, associated with either 1) two or more typical locations of scabies, or 2) a household member with itching has a 100% sensitivity and a 97% specificity for the diagnosis.

The infected person and close contacts should be treated at the same time, regardless of whether symptoms are present.

Permethrin (5% cream) is given as a single overnight application. A meta-analysis reported it was more effective than lindane. The CDC recommends it as first line treatment.

Topical treatments may be poorly tolerated by some patients. They are messy, may be difficult to apply, and may cause burning and stinging. Ivermectin (*Stromectal*: 3 mg tablets) has been used for several parasitic infections. Several controlled trials have assessed efficacy of a single dose (200 ug per kg). One trial compared ivermectin with permethrin. Ivermectin cured 70%; permethrin cured 98%. A second dose of ivermectin two weeks later cured 95%. When oral therapy is prescribed, the CDC recommends a dose of 200 ug/kg repeated two weeks later. Trials suggest that ivermectin is safe.

Scabies is prevalent among the homeless and among persons visiting free clinics, which are supported by many communities.

SCREENING

"All Screening Programs Do Harm; Some Do Good As Well"

4-7 SHOULD WE SCREEN FOR DEPRESSION? A Review of Screening Programs

This article presents 9 key criteria of UK National Screening Committee for screening.

(Read the abstract and the article. RTJ)

For screening for depression, the article concludes: "Opportunistic screening and population level screening for depression do *not* fulfill the criteria of the UK Screening Committee."

The use of these criteria indicates that screening for depression is unlikely to be a clinically effective or cost effective way to improve the mental wellbeing of the population. Screening alone cannot improve the management and outcome of depression unless systems to manage the depression are available.

I believe this presents an important consideration for primary care. The criteria considerably restrict screening.

Strictly defined, screening applies only to persons who have no signs or symptoms of the condition in question. This implies that the condition screened for, in the population selected, reflects only the prevalence of that condition in that population.

The borderline between screening and testing is ill defined.

I believe that most screening in primary care practice is applied to persons who have at least some pre-test probability of having the condition screened for. The "screen" then becomes a "test". A positive result would indicate a higher post-test probability of having the condition.

I believe screening in the USA is overdone. Primary care clinicians should be circumspect. They should make the patient aware of risks (including creation of considerable ongoing anxiety) as well as benefits of a screen. The patient should be willing to proceed to further investigation and treatment if the screen is positive. Adequate referral and treatment should be available.

I note that some entrepreneurs still come to town offering "Life Line Screening". All residents are invited to participate. The screens (for a fee) include "stroke/carotid artery screening, abdominal aortic aneurysm screening, and peripheral artery disease screening". This type of screening meets few of the UK National Screening Committee key criteria. I believe they do more harm than good.

SOMATIZATION

Begin Consideration of Both Biomedical and Psychosocial Causes at the Onset of A New Consultation

2-1 SOMATIZATION: *A Joint Responsibility of Doctor and Patient*

Most studies of somatization focus on patients' characteristics. There is a widespread belief that inappropriate symptomatic treatment has to be attributed to patients' beliefs that symptoms are caused by physical

disease, their insistence on biomedical intervention, and their denial of psychosocial needs. The possibility that doctors play a part has been largely ignored.

A detailed analysis of general practice patients with unexplained symptoms found that physical interventions were proposed more often by doctors than by patients. Almost all patients provided clues to their psychological needs. Most doctors suggested that one or more physical diseases might be present. The authors conclude that the explanation for the high level of physical intervention in these patients lies in doctors' responses rather than patients' demands.

Some studies show that most doctors adapt their biomedical interventions at least partly to presumed patient preferences. They may overestimate their patients' wishes in this regard, particularly regarding prescriptions and referrals.

The mantra "First of all, do no harm" seems to be replaced by "First of all, don't miss a medical diagnosis".

The editorialists conclude that a solution may lie in a comprehensive approach right from the start in which a biomedical track and a psychosocial track are jointly explored. This may give the patient confidence that all biomedical needs are rightly addressed while at the same time the floor is open for discussing psychological issues.

Primary care clinicians—Do you agree that we are partly responsible for the overuse of tests and consultation—not only for patients with suspected somatization,, but for patients in general ?

These patients are indeed suffering. How best can primary care clinicians help them? I believe mainly by listening to the patient. The art of medicine is indeed long and difficult.

SPIRITUAL CONCERNS—END OF LIFE

One Simple Non-Threatening Question To Probe Spiritual Concerns At The End Of Life.

1-1 ARE YOU AT PEACE?

Acknowledging the importance of emotional and spiritual issues at the end of life is an important component of compassionate and comprehensive palliative care. Some physicians may question the appropriateness of their role in probing patients' spiritual distress, as well as the practicality of addressing such issues in the time-limited setting of usual practice. Yet, a patient's spirituality often influences treatment choices, and endows personal resources during serious illness.

Respondents (n = 248) completed several questionnaires which assessed quality-of-life at the end of life. All had advanced cancer, severe heart failure, severe COPD, or renal failure.

Examined distributions of several religious and non-religious alternative wordings—"at peace with God"; "at peace with my personal relationships"; "at peace with myself". To promote inclusiveness, the final wording was the simple question--"Are you at peace?"

Ninety % agreed with the importance of "coming to peace with God". Ranked equally, and as most important, "freedom from pain" and "being at peace with God". Items measuring peacefulness correlated highly with having a chance to say goodbye; with making a positive difference in the lives of others; giving others gifts and wisdom; sharing deepest thoughts; and having a sense of meaning in life.

Feeling at peace was strongly correlated with emotional and spiritual well-being.

"The results of this study suggest that the concept of patients' sense of being at peace may be a point in which to initiate a conversation about emotional and spiritual concerns in a non-threatening manner."

Spirituality has been defined as the search for the ultimate meaning and purpose of life. This often involves a relationship with the transcendent. Emotional and spiritual well-being underpin the broadly worded construct of "being at peace".

Patients' end-of-life experiences are constructed by multidimensional layers of relationships of physiological and biochemical processes, cognitive understandings, interpersonal connections, and bonds to the transcendent.

Asking patients about the extent to which they are at peace may offer a gateway to assessing spiritual concerns. Although these issues may be heightened at the end of life, it may influence medical decisions throughout a lifetime of care.

Read the original!

Being at peace is important at all phases of life. Asking a non-terminal 30-year old if he is at peace may lead to introspection and benefit.

STROKE

"A Major Modifiable Risk Factor" Eat Five or More Fruits and Vegetables Daily

1-8 FRUIT AND VEGETABLE CONSUMPTION AND STROKE

Epidemiological studies suggest that increased consumption of fruits and vegetables may be associated with reduced risk of stroke. The extent of the association is uncertain.

This meta-analysis assessed the relation quantitatively.

. Literature search entered 8 studies which met inclusion criteria. (Over 257 000 individuals)

Determined frequency of fruit and vegetable intake and correlated it with frequency of incident stroke.

Grouped consumption into 3 categories: 1) less than 3 servings daily; 2) 3 to 5 servings daily, and 3) more than 5 servings daily. The standard serving was 0.5 cup.

Average follow-up = 13 years

Relative risk of stroke:

Less than 3 servings	1.00
3 to 5 servings	0.89
More than 5	0.74

Fruit and vegetables had a protective effect on both ischemic and hemorrhagic stroke.

Increased fruit and vegetable intake in the range commonly consumed (over 5 servings daily) was associated with reduced risk of stroke.

The Population Impact Of The MetS Is Much Greater.

1-9 METABOLIC SYNDROME COMPARED WITH TYPE 2 DIABETES AS A RISK FACTOR FOR STROKE. ***The Framingham Offspring Study***

This study compared the risk of stroke in patients with DM2-alone, and with MetS-alone. Estimated the population-attributable risk of stroke associated with each.

Over 10 years, the relative risk (RR) of stroke of persons with MetS-alone (compared to those without either DM2 or the MetS) = 2.10. The RR of stroke in persons with DM2-alone was 2.5.

The prevalence of the MetS-alone in the general population was much greater than prevalence of DM2-alone. Consequently, the population-attributable risk of stroke associated with the MetS-alone was larger than the risk of stroke associated with DM2. This was despite the higher RR of stroke associated with DM2-alone

Hyperinsulinemia and insulin resistance are accepted as prominent features of MetS. This suggests that, like impaired glucose tolerance and impaired fasting glucose, MetS may signal a prediabetic state. In the Framingham Heart Study cohort, those with MetS had a 5-fold risk of developing diabetes.

Because MetS is much more prevalent than diabetes, the population impact of the syndrome is greater.

There is a great potential for substantial reductions in stroke risk in people with MetS by treatment of its components.

MetS-alone per 100 000 population	*Risk of stroke over 10 years*	*Absolute number experiencing stroke*
22% X 100 000 = 22 000	*37/461 = 0.08 or 8%*	*22 000 X 0.08 = 1765*

DM2 per 100 000 population	*Risk of stroke over 14 years*	*Absolute number experiencing stroke*
5% X 100 000 = 5000	*12/99 = 0.121 or 12.1%*	*5000 X 0.121 = 606*

Thus, stroke occurred more than 3 times as frequently in persons with MetS-alone as with DM2-alone.

One in four adult Americans has MetS. This is a national disgrace. And a massive Public Health problem. Primary care clinicians bear a great responsibility for guiding patients for prevention, and for treatment once it is established. Clinicians should take the lead by preventing themselves from developing MetS.

Practical Pointers has reported many studies regarding the MetS. To refresh memory, the diagnosis requires 3 of 5 criteria to be present:

1) Elevated fasting Blood glucose -- 100-125 mg/dL

2) BP 130/85 or over, or treatment with antihypertension medication

3) Triglycerides 150 and over

4) HDL-c < 40 in men and < 50 in women

5) Waist circumference > 88 cm in women and > 102 cm in men.

Not all 5 criteria carry equal weight in their association with risk. It is becoming more evident that abdominal obesity may be the greatest culprit. It may carry the greatest potential for development of insulin resistance and hyperinsulinemia.

Should We Treat With Drugs Alone, and Ignore Other Risk Factors?

5-8 ASPIRIN PLUS DIPYRIDAMOLE VERSUS ASPIRIN ALONE AFTER CEREBRAL ISCHEAMIA OF ARTERIAL ORIGIN

This remarkable multicountry, secondary prevention trial randomized over 2700 patients for 3.5 years to aspirin alone (median 75 mg daily), or aspirin + dipyridamole (200 mg twice daily, mainly as extended release). All had experienced a TIA or a non-disabling (*minor)* ischemic stroke.

At randomization, 18% had diabetes; 60% had hypertension; 47% had hyperlipidemia; and 36% smoked.[1]

More patients on the combination discontinued trial medication (470 vs 184) mainly due to headache, a common adverse effect of dipyridamole.

Primary outcome = a composite of non-fatal stroke, non-fatal myocardial infarction, or death from vascular causes.

Results (3.5-y)	Combined A + D (n = 1316)	Aspirin alone (n = 1376)	Absolute diff	NNT 3 y
Primary outcome	13%	16%	3%	33

The authors conclude: "Our findings show that the combination of aspirin and dipyridamole is more effective than aspirin alone in the prevention of new serious vascular events in patients after non-disabling cerebral ischaemia of presumed arterial origin."

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1 *There was no mention about efforts to treat these major risk factors. I presume the investigators intervened at least in some patients. Trials such as this, which randomize subjects to drug vs drug, or drug vs no-drug,, consider only the effect of the drug. This is not the way primary care works. In the real world of practice, every effort is made (or should be made) to reduce all risk factors in addition to prescribing a presumably helpful drug. I believe there would have been a considerable difference in outcomes in this study (with less benefit from the combined group vs aspirin alone) if all risk factors were treated. And, a much larger cohort of subjects would have been needed to determine any difference in outcome.*

Should primary care clinicians advise the combination to this subset of patients? I believe that many primary care patients would not adhere to the regimen for 3 years. A large number would withdraw.(Primary care patients are much less adherent than subjects in studies.) In addition, others would withdraw because of headache and bleeding. Informing patients that, over 3 years, there is only one chance in 33 of benefit at a cost of over $2300 would discourage some.

TELEPHONE FOLLOW-UP

An Expression Of Care And Caring

5-2 EFFECT OF TELEPHONE CONTACT ON FURTHER SUICIDE ATTEMPTS IN PATIENTS DISCHARGED FROM AN EMERGENCY DEPARTMENT

Psychiatrists contacted patients by telephone one month after an attempted suicide. This reduced the proportion of patients who re-attempted suicide. Read the full abstract.

This, of course, does not apply to primary care. I abstracted the article to comment on an application which is basic to an expression of care and caring in primary care.

Patients, especially those who have had some serious illness or have been referred to specialists by the primary care clinician (PCC), are most grateful when they receive a follow-up phone call from the PCC inquiring about their progress and status. Such contact will enhance the patient-doctor relationship. Patients will remember it. I believe it is well worth the time spent. Similar expression of care and caring can be expressed if, after the death of a patient, the PCC makes a personal visit to the family.

THYROID DISEASE

Subclinical Hyper-Thyroidism was Associated with an Increased Incidence of Atrial Fibrillation

Subclinical Hypo-Thyroidism was not Associated with Adverse Cardiovascular Events.

3-7 THYROID STATUS, CARDIOVASCULAR RISK, AND MORTALITY IN OLDER ADULTS

Reportedly, even mildly altered thyroid status affects cholesterol levels, heart rhythm and rate, ventricular function, risk of coronary artery disease, and cardiovascular mortality. The relationship is not well defined.

The Cardiovascular Health Study determined the relationship between baseline thyroid status and incident atrial fibrillation **(AF),** incident cardiovascular disease, and mortality in older men and women followed for 13 years.

Enrolled over 3223 community-dwelling adults (all over age 65; mean = 72) in 1989-90.

Divided subjects into 5 groups:

A. Overt hyper-t—thyrotoxicosis (elevated FT4; low TSH [less than 0.10]. Only 4 subjects of 3200 fit this category. They were eliminated from the study.)

B. Subclinical hyper-t. (Normal FT4; low TSH)

C. Euthyroidism (Normal FT4; normal TSH)

D. Overt hypo-t. (Low FT4; elevated TSH)

E. Subclinical hypo-t (Normal FT4; TSH elevated.)

	Number (of 3223 subjects)	%
Overt hyper-t	4	
Subclinical hyper-t	47	1.5
Euthyroid	2639	82
Subclinical hypo-t	496	15
Overt hypo-t	51	1.6

Subjects with subclinical hyper-t: A greater incidence of AF compared with euthyroid subjects (67 events vs 31 per 1000 person-years). No statistical differences in incidence of cardiovascular outcomes and death.

Subjects with subclinical hypo-t and overt hypo-t: No statistical difference in outcomes.

“Our results clearly show a relationship between low TSH levels and atrial fibrillation incidences in older individuals with endogenous subclinical hyperthyroidism, including those with TSH levels between 0.1 mU/L and 0.44 mU/L.”

There was no relationship between subclinical hypo-t or overt hypo-t and incident atherosclerotic disease, cardiovascular mortality, or all-cause mortality.

"Our findings suggest that, if endogenous subclinical hyperthyroidism is detected, older individuals may benefit from treatment to prevent atrial fibrillation."[1]

Conclusion: There was an association between subclinical hyperthyroidism and development of AF. There was no association between subclinical hypo-t, or overt hypo-t, or subclinical hyper-t and other cardiovascular disease and mortality.

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1 *What treatment? I am curious, how do thyroidologists approach this problem? Would the investigators suggest radioactive iodine in these patients?*

I suspect that iatrogenic subclinical hyper-t is more common than endogenous.

I abstracted this study in detail to point out:

1) The high prevalence of subclinical hypo-thyroidism in an unselected group (15%).

2) To ask—What should be done with individuals with abnormalities?

Patients with subclinical hypo-t should be followed closely. They often develop overt clinical hypothyriodism.

TOBACCO

"One Billion Deaths from Tobacco in the 21st Century"

5-3 TOBACCO: Deadly in Any Form or Disguise

In 1950, Doll and Hill, in their study of British doctors, were the first to determine that tobacco is harmful. The follow-up of the study closed in 2004, when all the participating smokers were dead, and some 6000 non-smokers remained alive. The data suggest that between one half and two-thirds of the persistent smokers died because of their habit.

"No form of tobacco use has yet been shown to be safe, and the world would be a healthier place without such products." Cigarettes and other forms of burnt tobacco, including pipes and cigars, are carcinogenic. Exposure to environmental tobacco smoke is carcinogenic. Exposure to smokeless tobacco is carcinogenic.

In the USA, there are still about 1 million new smokers a year. Of these, about half will be killed by tobacco if they do not stop, and half of these deaths will be in ages 35-69. Around the world, it can be expected that the number of tobacco deaths will exceed 10 million every year unless 20 million current smokers stop. The effect of stopping is clearly beneficial in terms of limiting the increases in death from cardiovascular disease and chronic lung disease.

This commentary is signed by 34 international experts from 24 different countries. Does this report exaggerate the problem? If it does, I believe the exaggeration is minimal.

This commentary is timely. The Surgeon General of the U.S. just issued a very strong warning about passive (involuntary; secondhand) smoking. More than 120 million Americans are regularly exposed to this hazard. "Secondhand smoke is a serious health hazard." (The Charlotte Observer, June 28, 2006)

Would it be helpful if primary care clinicians posted this article in their waiting rooms and distributed it to select patients? It is never too late to stop!

"Current Smoking And Exposure To Passive Smoke Were Positively Associated With Increased Risk"

5-4 ACTIVE AND PASSIVE SMOKING AND DEVELOPMENT OF GLUCOSE INTOLERANCE AMONG YOUNG ADULTS: The CARDIA Study

This prospective cohort study, begun in 1985-86 and continued for 15 years, assessed whether active and passive smokers (over 4500 men and women age 18-30 at baseline; median age = 25) are more likely to develop clinically relevant glucose intolerance or diabetes.

No subjects had glucose intolerance at baseline (defined as fasting glucose > 100 mg/dL, or taking antidiabetes drugs).

Seventeen % of participants developed glucose intolerance at fifteen years. Three % developed diabetes.

After adjustment for possible baseline confounders, there was a graded association between smoking exposure and development to glucose intolerance:

	% glucose intolerance	Hazard ratio
Current smokers	22%	1.65
Previous smokers	14%	1.17
Never smokers; passive smoke	17%	1.35
Never smokers; no passive smoke	12%	1.00

Pack-years of smoking was associated with risk of developing glucose intolerance—increasing by 18% for every increase of 10 pack-years.

Tobacco exposure was associated with development of glucose intolerance over a 15-year period with a dose-response effect. Passive smoke is a risk factor in never-smokers.

This is my first encounter with this association. This report is timely. The Surgeon General of the United States just issued a strong statement describing the dangers of passive smoke, and warning against it.

Tobacco smoke has been associated with increased risk of macular degeneration in the elderly. I do not know if there is an association with passive smoke.

TRANS FAT

4-1 TRANS FATTY ACIDS AND CARDIOVASCULAR DISEASE: Review Article

Trans fats are formed during "partial hydrogenation" of vegetable oils (an industrial process). This converts the oil into semisolid form for use in margarines, commercial cooking, and manufacturing processes. The food industry favors trans fats because their shelf life is long, they are stable during deep-frying, and may enhance palatability of baked goods and sweets.

The average consumption of trans fats in the USA is 2% to 3% of total calories consumed.

The Department of Agriculture made limiting intake of trans fats a key recommendation in the new food pyramid. Consumption should be limited to below 1% of total energy intake.

The FDA has ruled that the nutrition labels of conventional foods and supplements must indicate the content of trans fats. (*Consumers should remember to check the "Nutrition Facts' on labels. RTJ*)

These actions were prompted by evidence that trans fats increase the risk of coronary heart disease by several different mechanisms:

A. Adverse effect on serum lipids.

B. Promotion of systemic inflammation.

C. Trans fats may also cause endothelial dysfunction.

"On a per-calorie basis, trans fats appear to increase the risk of CHD more than any other macronutrient." Even at low levels of consumption (1 to 3 percent of calories), a substantially increased risk occurs.

Trans fats have no intrinsic health value above their caloric value. Thus, their intake may result in considerable potential harm with no apparent benefit.

The potential harm is clear. Adverse effects are seen even at low intakes—1% to 3% of total energy (~ 20 to 60 calories; 2 to 7 grams for a person consuming 2000 calories daily).

"Thus, complete or near complete avoidance of industrially produced trans fats—consumption of less than 0.5 percent of total energy intake—may be necessary to avoid adverse effects."

Avoidance will depend on consumers' decisions to choose foods free of trans fats. This depends on knowledge of the type and quantity of oils used. *(Again, read the label. In restaurants, choose foods less likely to contain trans fats. RTJ)*

About 20% of CHD events could be prevented by total avoidance of trans fats and replacement with cis unsaturated fats.

Elimination of trans fat (as much as possible) should be considered a major goal for reducing risk of CHD. Obviously, daily consumption of 2 grams (over 1% of total calorie intake) is very easy.

Fifty Percent of The Servings Contained More Than 5 Grams Per Serving—The Amount Associated With A 25% Increase in Risk Of Ischemic Heart Disease

4-2 HIGH LEVELS OF INDUSTRIALLY PRODUCED TRANS FAT IN POPULAR FAST FOODS

"The daily intake of about 5 grams of trans fats is associated with a 25 percent increase in the risk of ischemic heart disease."

This study determined the content of industrially produced trans fat in fast foods purchased in 2004 and 2005 in 20 countries. The table (p 1651) illustrates the amounts of trans fat in McDonald's and KFC outlets in a large serving of french fries and chicken.

The content of trans fat in a large serving of french fries varied from less than 1 gram in Denmark to 7 grams in New York City and 12 grams in Hungary. Fifty percent of the servings contained more than 5 grams—the amount of daily intake associated with a 25% increase in risk of ischemic heart disease.

Large variations were observed within the same chain in the same country.

As the general public becomes more aware to the risks, I believe that fast food companies and food manufacturers can (and may have to) lower the trans fat content of their foods. The fact that the trans fat content varies markedly in different countries and even within a given country suggests that consumers will accept foods prepared with oils containing lower amounts of trans fats.

McDonalds is trying. I recently picked up several brochures describing their efforts to promote balanced eating. Their "McDonald's Nutrition Facts" lists foods prepared with "partially hydrogenated" cooking oils.

Tables list trans fat content	*Grams*
Plain hamburger	*0.5*
Big Mac	*1.5*
Small french fries	*2.5*
Large french fries	*6.0*
Biscuit	*5.0*
Deluxe breakfast	*11*
Warm cinnamon roll	*4.5*
Baked apple pie	*4.5*
Chocolate chip cookie	*1.5*

I enjoy McDonalds and KFC. I believe they will attempt to lower trans fat content. I will watch developments carefully, while I avoid ingestion of trans fats as much as possible.

TUBERCULOSIS

Fewer False Negative and False Positive Tests

1-11 CDC RECOMMENDS NEW TUBERCULOSIS BLOOD TEST. QuantiFERON-TB Gold

The QuantiFERON-TB Gold in vitro test replaces the older QuantiFERON-TB test which is no longer available. The CDC believes it is more accurate and represents a considerable advance over the original QuantiFERON-TB test. (MMWR December 16, 2005)

The test detects the release of interferon-gamma in fresh heparinized whole blood from sensitized persons when it is incubated with two synthetic peptides which simulate two proteins present in *M tuberculosis.*

VENOUS THROMBOEMBOLISM

1-13 VENOUS THROMBOEMBOLISM—18 POINTS

(Review articles appear frequently. They are interesting and informative, but long and difficult to abstract. This is an experiment. These few points emphasize the important and serve as a memory-jogger. Is it helpful? I would appreciate feed-back. Is it helpful? RTJ)

A Promising Anticoagulant. Long-Term Efficacy Not Established.

2-10 EFFICACY AND SAFETY OF FONDAPARINUX FOR THE PREVENTION OF VENOUS THROMBOEMBOLISM IN OLDER ACUTE MEDICAL PATIENTS

"Most patients who die from pulmonary embolism **(PE)** as a complication of being admitted to hospital are medical patients." Around 10% of deaths are due to PE.

Fondaparinux (*Arixtra*; Glaxco SmithKline) is a synthetic, selective inhibitor of factor Xa. It effectively reduces postoperative venous thromboembolism **(VTE)** after orthopedic surgery.

This study determined the short-term efficacy and safety of fondaparinux in older, acutely ill *medical* inpatients. Randomized within 48 hours to: 1) fondaparinux, or 2) placebo.. Doses were given subcutaneously daily (2.5 mg fondaparinux or 0.5 mg saline).

A. Primary efficacy outcome *for first 15 days only*:

	Fondaparinux	Placebo
Any VTE	18	29
Proximal deep vein thrombosis	5	7
Distal deep vein thrombosis	13	22
Fatal PE	0	5
Total	18/321 (5.6%)	34/323 (10.5%)

(NNT to prevent one VTE = 20.)

B. Symptomatic VTE *up to day 32*:

	Fondaparinux	Placebo
Symptomatic deep vein thrombosis	0	0
Non-fatal pulmonary embolism	1	4
Fatal pulmonary embolism	3	7

Ten *additional* cases of PE occurred during follow-up after day 15—4 in the fondaparinux group, 6 in the placebo group. (Three in the fondaparinux group were fatal.).

Major bleeding occurred in one patient in each group. (0.2%) [1]

Two thirds of the clinically apparent events and half of the fatal PE were observed *after* the initial 6 to 14 day study period. This supports the need to evaluate extended prophylaxis in medical patients.[2]

I abstracted this article mainly to introduce what may become a major breakthrough. Two new oral Xa inhibitors are in the works.

1 *If the risk of major bleeding is indeed lower with fondaparinux, it would be a major benefit. Watch for further studies.*

2 *Note that the study focused on outcomes over 2 weeks only. The risk of VTE in these very ill older patients extends far beyond. The investigators note that VTE occurred frequently after the study period. Some were fatal. The question remains: How long must fondaparinux be continued in these medical patients? And for how long? . Duration of therapy for only 2 weeks adds relatively little overall protection.*

VITAMIN D

Vitamin D Deficiency During Pregnancy Is Associated With A Deficit In Bone-Mineral Accrual In The Children

1-6 MATERNAL VITAMIN D STATUS DURING PREGNANCY, AND CHILDHOOD BONE MASS AT AGE 9 YEARS

This study tested the hypothesis that low vitamin D levels in women during pregnancy have persisting effects on bone mass in their children.

Measured serum 25(OH)-vitamin D at a mean of 34 weeks of pregnancy. Classified vitamin D levels as being deficient if the serum level was under 11 ug/L and as insufficient if level was 11-20. Normal > 20.

Nine years later, measured children's' bone mineral content **(BMC)** and areal bone mineral density **(BMD**) by dual energy X-ray absorptiometry.

Eighteen % of women had insufficient vitamin D levels, and 31% had deficient levels. (Half of all women.)

At age 9, children of mothers with reduced concentrations of vitamin D had reduced whole-body and lumbar spine bone mass compared with children of mothers with normal serum vitamin D.

Maternal UV exposure during late pregnancy varied by season and predicted serum concentrations of D. (Mean levels in winter = 14 ug/dL; summer = 30 ug/dL). Children of mothers whose third trimester occurred in summer had higher BMD than those whose third trimester occurred in winter.

Use of vitamin D supplements predicted maternal concentrations of vitamin D. (In this cohort, only 15% of mothers took supplements containing vitamin D.) Their children at age 9 had significantly greater whole-body BMD than children of non-users.

"Our results suggest that vitamin D insufficiency (or deficiency) during late pregnancy is associated with a deficit in bone-mineral accrual in their children which persists to age 9."

Vitamin D deficiency and insufficiency were common in these pregnant women. Supplementation could lead to enhanced peak bone mineral accrual in their children, and lead to reduced risk of fragility fracture later in life.

Can these deficient children catch up as they grow older? I believe good nutrition including adequate calcium intake and vitamin supplementation (especially D) will allow catch up.

Vitamin D deficiency is highly prevalent in developed countries in northern latitudes in the winter. I believe it is by far the most common vitamin deficiency. Supplements are required life long.

Is this the final word on calcium + vitamin D supplementation to reduce risk of fracture ?

2-4 CALCIUM PLUS VITAMIN D SUPPLEMENTATION AND RISK OF FRACTURES IN OLDER WOMEN

This trial tested the hypothesis that calcium + vitamin D **(C + D)** supplementation, begun at an advanced age in women, would lower risk of hip fractures and other fractures as compared with placebo.

The Women's Health Initiative recruited over 36 000 postmenopausal women age 50 to 79 (mean age = 62 at baseline). All were living in the community and were considered healthy.

Randomized to: 1) 1000 mg calcium + 400 IU vitamin D daily, or 2) placebo.

Bone mineral density was greater in the calcium + vitamin D group at year 7 by 1%.

Fracture rate overall*	Ca + D	Placebo
Hip	175	199
Vertebral	181	197
Forearm of wrist	565	557
Total	2102	2158

(*Intention-to-treat. No statistical difference between groups.)

Among women who were adherent (ie, took at least 80% of their study medication), C + D supplementation resulted in a 29% reduction in hip fracture—68 in the C + D group vs 99 in the placebo group (95% confidence interval = 0.52-0.97—statistically significant).

"The trial demonstrated that calcium with vitamin D supplementation diminishes bone loss at the hip, but the observed 12 percent reduction in the incidence of hip fracture (the primary outcome) was not statistically significant." "It is plausible that there was a benefit only among women who adhere to the study treatment." Only 59% of women were still taking the intended dose of the study medication at the end of the trial.

Although the statistically null primary effect argues against recommending universal calcium with vitamin D supplementation, the findings provided evidence of a positive effect of calcium with vitamin D on bone health in older postmenopausal women

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I would amend the conclusion to state that calcium and vitamin D supplementation did not significantly reduce hip fracture when begun at age 62. I would not expect much reduction in fractures in women when C + D supplementation is begun long after the menopause. Intakes of C and D are almost universally deficient in the USA at all ages. Efforts to develop and maintain healthy bone structure are a life-time endeavor. Primary care clinicians should ensure their patients achieve adequate intakes beginning in childhood.

The benefit/harm-cost of C + D supplementation is, I believe, very high. Entering menopause with healthy bones will reduce hip fractures and alleviate the frequency of disabling kyphosis which plagues many older women.

WARFARIN

Once Burned; Twice Shy

1-2 IMPACT OF ADVERSE EVENTS ON PRESCRIBING WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

This study quantified the influence of physicians' experiences of adverse events in patients for whom they had prescribed warfarin on their subsequent prescribing practices.

Considered patients who experienced severe gastrointestinal bleeding or hemorrhagic stroke while taking warfarin during the 120 days before admission to the hospital. Determined likelihood that the doctor who prescribed the warfarin would prescribe it to the next patient presenting with AF. (If a physician treated a patient

with warfarin and the patient had serious bleeding, would this experience influence prescribing warfarin for a second patient who has AF?)

Also considered patients with AF who experienced an ischemic stroke during the preceding 120 days for whom the doctor had *not* prescribed warfarin. Determined the likelihood that the doctor would prescribe warfarin to the next patient with AF who consults him.

Over 500 physicians treated a patient with AF who had major bleeding while on warfarin, and then treated another patient with AF within the next 90 days.

The odds that a physician would prescribe warfarin for a second patient were 21% lower after a first patient experienced bleeding. (Some physicians were reluctant to again prescribe warfarin.)

Conversely, there were no significant changes in warfarin prescribing after a patient had a stroke while *not* taking warfarin. (Physicians were *no more likely* to prescribe warfarin for a second patient with AF despite this adverse outcome.)

“Doctors are neither passive recipients of, nor simple conduits of, clinical evidence.” We conduct an “inner consultation” with evidence, analyzing it in both a logical and intuitive way. In doing so, we are more likely to recall events which are more easily recalled. And the “chagrin factor” tends to make doctors avoid actions that cause them hassle.

Patients conduct similar internal consultations, adding the experience of a consultation to their previous intellectual and emotional understanding of illness.

“Statistical experience” and “clinical experience” guide consultations. These are not enough to clarify the dynamic interaction between patient and doctor. A third dimension is “personal significance”, a concept that captures the reciprocity of the evaluation and interpretation of a new idea by a doctor and patient together. At stake here is something quite profound, and poorly accepted within the medical community—the personal participation of the knower in all acts of understanding. Comprehension is neither an arbitrary nor passive act. It requires tacit skills of judgment.

“In medical consultations there are two participants, both personally knowing, both passionately participating, but from different perspectives, different “somewheres”. The outcome of their interaction in the form of clinical decision is an emergent property of two ways of knowing: biomedical and biographical.

The study illuminates this murky area and provides convincing evidence that within each doctor, these two ways of knowing compete for influence.

Patient’s prior experience plays a major role in acceptance and compliance with therapy. This study points out that doctors respond to prior experience as well.

Patients and doctors consider adverse events due to commission more seriously than adverse events due to omission. When a patient with AF bleeds while he is taking warfarin, warfarin and the doctor who prescribes it get the blame (whether at fault or not). When the patient experiences an ischemic strike, there is doubt about whether warfarin would have prevented it. (It may not have prevented it.) Warfarin and the doctor would less likely be blamed.

Prior experiences and “personal knowledge” do indeed influence subsequent practice.

Do not patients' "personal beliefs" have a much greater influence on their acceptance and compliance with treatments? Eg, belief in a placebo; belief in many "alternative medications"; belief in the advertisements of drug companies; beliefs based on ethnicity and family lore, belief in anecdotal experiences and advice of family and friends; belief in health advice given in the press, on TV, and in the Internet.

Do not physicians' "personal beliefs" influence the treatments they advise to a greater extent than evidence-based therapy? Eg, belief in the latest advertised drug; belief in the suggestions of colleagues given in curbside consultations; belief based on their educational experiences and past training which have become outdated; belief in anecdotal evidence from small, unsubstantiated observational studies, and even "alternative medicine".

WEIGHT LOSS PROGRAMS

"At 12 Months, Only 25% Of The Original Sample Were Still Keeping Their Allocated Diets"

6-7 RANDOMIZED TRIAL OF FOUR COMMERCIAL WEIGHT LOSS PROGRAMS IN THE UK

The BBC "Diet Trials"

"Most adults in the United States diet at some time." Long-term success rates are poor.

This randomized unblinded trial considered 4 diets available in the UK vs a control group:

A. Dr Atkins' new diet revolution (a self-monitored low carbohydrate diet.)

B. Weight Watchers (an energy controlled diet with weekly group meetings.)

C. Slim-Fast (a meal replacement approach.)

D. Rosemary Conley's eat yourself slim diet and fitness plan (a low fat diet and a weekly group exercise class.)

All 4 diets resulted in about an equal weight loss over 6 months: (Intention-to-treat basis)

	Atkins	WW	Slim-Fast	Rosemary	Controls
Loss (kg)	6	7	5	6	Gain of 0.6 kg

People who kept their allocated diet lost about 10% of their weight despite some weight rebound. "These results provide information about the 'best effect' that the most highly motivated subjects may hope to achieve over one year. "

Would adopting a revolving diet plan (ie, switching from one to another after a month) benefit some people?

The only proven remedy for obesity is bariatric surgery.

WESTERN MEDICAL TRADITION (Book Review)

Suppose You Could Have Lived At Any Time In Human History. When Would It Be?

6-13 THE WESTERN MEDICAL TRADITION 1800 to 2000: *Book Review*

Suppose you could have lived at any time in human history. When would it be? The age of Pericles? The dawn of Christianity? Renaissance Europe? The Enlightenment? Victorian Britain? Take your pick.

A Canadian radio discussion of this possibility fell distinctly flat when all the panelists instantly agreed that our time is the best time to come into the world. The reason: modern health care and the capacity of the modern state to make it available to ordinary people.

The Western Medical Tradition 1800 to 2000 (Cambridge University Press, 2006) is authored by 5 editors associated with the *Wellcome Trust Centre for the History of Medicine.*

Read the full abstract or the original.