This index is a reference document based on articles abstracted from 6 flagship journals July – December 2008. It provides a means of recalling to memory, in an evening or two, what the editor considered new and important for primary care.

The numbers in the brackets refer to the abstract. For example, [8-6] refers to the sixth article abstracted in August.

It consists of 4 parts:

1) “Practical Clinical Points”: This provides an instant reminder of points of clinical interest and importance which primary care clinicians may wish to advise patients about, consider, and be aware of. Some points are new; some emphasize older points.

2) “Medical Subject Headings” (MeSH): A list of 54 medical subject headings from alcoholism to vitamin D, arranged alphabetically.

3) “Highlights of Abstracts and Editorial Comments” section: linked alphabetically to each MeSH. (There may be several articles listed under a MeSH.) The highlights contain a condensation of each abstract. The Editorial Comments are those of the editor alone, based on his years-long experience as a practicing primary care internist and as editor and publisher of Practical Pointers for Primary Care.

4) The abstract itself may be accessed from the monthly issues which provide more detailed information, and the citation.

Monthly issues for the past 10 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
ADVISE

End-of life discussions with terminally ill patients. This offers them an opportunity to define their goals and expectations of medical care. It may lead to less aggressive care, greater acceptance, and better quality-of-life for them and their bereaved caregivers. [10-3]

Increased calcium supplementation (1200 mg) in men, as well as women, to increase bone mineral density [11-3]

Use of human papilloma virus testing in addition to cytology to screening for cervical cancer. [10-2]

Pregnant women to take a flu shot. [10-4]

Adoption of lifestyle factors (healthy diet, not smoking, weight control, moderate alcohol consumption, and a physical activity program). It extends lifespan and lowers all-cause mortality [9-11]

Adoption of a Mediterranean diet. It significantly decreases mortality, cardiovascular disease, and cancer. [9-3]

Eating slowly, chewing food well, and not eating until full. This may lead to better weight control. [11-4]

Bisphosphonates and supplementation with calcium and vitamin D for men as well as women with osteoporosis. And for those at risk for developing osteoporosis. [9-7]

Do not screen men over age 75 for prostate cancer with PSA. Discuss potential benefits and known harms of PSA screening in men younger than age 75. “Think twice or even 3 times” before screening [12-7]

Young smokers that, if they continue to smoke, as they age their lives will be 10 years shorter, and they will feel 10 years older. [10-1]

CONSIDER

Routine screening for depression in patients with coronary heart disease. [12-5]

Long-acting insulins at bedtime, added to oral agents, to improve control [10-7]

Paying more attention to the oral health of patients with diabetes [12-6]

A low-glycemic diet may moderately lower HbA1c levels [12-8]

Many generic drugs are clinically equivalent to brand-name drugs. [12-2]

Treat and prevent heart failure with preserved ejection fraction (aka “diastolic heart failure”) by treating co-morbidities. Control of BP is essential [7-2]
The possible adverse effects of preventive therapy [12-1]

Thrombolysis with alteplase is effective up to 3 to 4.5 hours after acute ischemic stroke [9-4]

**BE AWARE**

A program of physical activity may modestly improve cognition in patients with Alzheimer disease [9-8]

Optimal medical therapy may be a reasonable choice for patients with angina, instead of proceeding immediately to PCI, especially in patients with less severe angina. [8-8] [8-9]

The nonfasting apolipoprotein B / apolipoprotein A ratio may be superior to any of the cholesterol ratios in estimating risk of myocardial infarction. [7-1]

The new stool DNA screening tests for colon cancer are a non-invasive option. Colonoscopy remains the standard. [10-10]

After a negative colonoscopy, a 5-year interval is reasonable before re-screening. [9-6]

Socioeconomic status is an important risk factor for coronary heart disease. [12-4]

Hearing loss may be related to diabetes. [7-6]

Metformin and sulfonylureas may lessen risk of cardiovascular mortality in patients with diabetes. Rosiglitazone may increase risk. [10-5]

Incretins are a promising treatment for type-2 diabetes. [10-9]

It may take years for all adverse effects of new drugs to be known. [11-8]

Migraine with aura is associated with increased risk of major cardiovascular events. [8-6]

Psyllium, hyoscine, and peppermint oil may improve symptoms of irritable bowel syndrome. [12-3]

The “polypill’ concept is still alive. [10-11]

Primary care medicine is in crisis. It needs a rebirth. [11-1]

Spirituality is a part of what it means of be human. It is an important part of medical care. [8-2]

Non-fasting triglycerides are a risk factor for ischemic stroke. [11-6]

Low concentrations of vitamin D are a risk factor for hip fracture. Deficiency has been linked to many other conditions. [8-3]
ALCOHOLISM
ALZHEIMER DISEASE
ANGINA
ANKLE BRACHIAL INDEX
APOLIPOPROTEIN A AND B
ASPIRIN
ASTHMA
BEREAVEMENT
CALCIUM SUPPLEMENTATION
CERVICAL CANCER
COLON CANCER
COLON POLYPS
COLONOSCOPY
CORONARY ARTERY (HEART) DISEASE
C-REACTIVE PROTEIN
(See STATIN DRUGS [11-2])
DIABETES
DIAGNOSIS
DIASTOLIC HEART FAILURE
(See HEART FAILURE [7-2])
DIVERTICULAR DISEASE
DRUG TREATMENTS
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(See OBESITY [7-2])
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GENERIC DRUGS
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(See DIABETES [7-6])
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HIP FRACTURE
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HUMAN PAPILLOMAVIRUS
INFLUENZA
IRRITABLE BOWEL SYNDROME
LIFESTYLE
MEDITERRANEAN DIET
MIGRAINE
OBESITY
ORAL HEALTH
(See DIABETES [12-6])
OSTEOPOROSIS
PERCUTANEOUS CORONARY INTERVENTION

POLYPILL
PREVENTIVE THERAPY
PRIMARY CARE MEDICINE
PROSTATE CANCER

RENAL OUTCOMES WITH TELMISARTAN AND RAMIPRIL

ROSUVASTATIN

(See STATIN DRUGS [11-2])

SMOKING
SPIRITUALITY AND PATIENT CARE
STATIN DRUGS
STROKE

TRIGLYCERIDES
(See STROKE [11-6])

VITAMIN
ALCOHOLISM

“Should Be Included Among The Standard History Questions”

11-11 THE CAGE QUESTIONNAIRE FOR DETECTION OF ALCOHOLISM: A Remarkably Useful but Simple Tool

“Some of the most remarkable advances in medicine are deceptively simple.” The CAGE questionnaire, published in the USA 25 years ago, is an example. Four simple questions have a major role in detecting alcoholism:

Have you ever:

1) felt the need to Cut down on our drinking?
2) felt Annoyed by criticism of your drinking?
3) had Guilty feelings about drinking?
4) taken a morning Eye opener?

A score of 2 or 3 indicates a high index of suspicion. A score of 4 is virtually diagnostic.

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This is one in the series “JAMA Classics”. I believe it merits a reminder.

ALZHEIMER DISEASE

Compares Favorably With The Improvement Reported With The Use Of Donepezil.

9-8 EFFECT OF PHYSICAL ACTIVITY ON COGNITIVE FUNCTION IN OLDER ADULTS AT RISK FOR ALZHEIMER DISEASE

Observational studies suggest that older people who are free of dementia, but report memory decline or show objective evidence of cognition impairment, are more likely to develop Alzheimer disease over time. Numerous observational studies have found that people who are physically active seem less likely than sedentary persons to experience cognitive decline and dementia later in life.

This trial was designed to test whether a 24-week home-based physical activity intervention would reduce the rate of cognitive decline among older adults at increased risk of dementia.

Randomized, controlled trial of 6-months of physical activity recruited volunteers (n = 170; mean age = 69) who reported memory problems, but did not meet criteria for dementia. 138 completed the trial.
Randomized to: 1) an education and usual care group (about memory loss, stress management, healthful diet, alcohol consumption, and smoking, but not physical activity), or 2) home-based program of physical activity.

Participants were encouraged to perform at least 150 minutes of moderate-intensity physical activity per week. (Three sessions of 50 minutes.)

Main outcome measure = change in Alzheimer Disease Assessment Scale (ADAS-cog) score over 18 months. Possible range = 0 to 70.

Intention-to-treat analysis:

A. End of 6-month intervention:
   Exercise group: ADAS-cog score improved by 0.26 points
   Control group: ADAS-cog score deteriorated by 1.04 points.

B. At 18 months:
   Exercise group: ADAS-cog score improved by 0.73 points.
   Control group: ADAS-cog score improved by 0.04 points.

(Differences between participants in the ADAS-cog score were statistically significant.)

“Unlike medication, which was found to have no significant effect on mild cognitive impairment at 36 months, physical activity has the advantage of health benefits that are not confined to cognitive function alone.” (Physical activity has been associated with lessening physical disability, depression, and incidence of falls, increased quality of life, and improvement in cardiovascular function.)

Importantly, the beneficial effects of physical activity were sustained during the 18 month follow-up period.

Conclusion: In adults with subjective memory impairment, a 6-month program of physical activity provided a modest improvement in cognition over an 18-month follow-up.

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*I doubt the improvement is clinically significant. However, there was no deterioration in the exercise group at 18 months. The intervention may delay deterioration thus decreasing the end-of-life dependence on others. It would be advisable to begin a program of exercise before aging prevents it.*

*Physical activity undoubtedly has many other advantages in the elderly. It has few adverse effects—much fewer than medications. Primary care clinicians should prescribe an exercise program for all patients, and adopt one themselves as a role model.*
ANGINA
“This Should Serve As Encouraging News To Patients With Coronary Disease.”

8-9 FINDING THE COURAGE TO RECONSIDER MEDICAL THERAPY FOR STABLE ANGINA

Coronary stents have revolutionized percutaneous coronary intervention (PCI) and have reduced the rate of complications and the need for repeat interventions. Clinician’s thresholds for PCI intervention have been markedly altered. Now, the presence of any angina can precipitate coronary angiography to detect amenable lesions, followed by PCI. Symptoms are no longer a prerequisite. Aggressive strategies for screening may reveal lesions that can be treated with PCI.

The therapeutic paradigm has reversed, with medical therapy generally reserved for those who have exhausted revascularization options.

The trial showed that, with contemporary medical treatment, the majority of patients had substantial improvements in health status that were sustained for several years. The rapid improvement with optimal medical therapy alone suggests that anginal medications are underused.

This underscores a major challenge to clinicians—how to successfully execute a strategy of optimal medical therapy in a health care system that provides strong financial rewards for PCI but few rewards for careful management of medications.

A very reasonable take home message from the trial is to pursue optimal medical therapy initially, and if it is ineffective, turn to PCI. Executing such a strategy will require “courage” to reconsider the algorithms of current care and the changes in policy that are necessary to give appropriate value to the effort that is required to manage medications optimally, and to monitor the health status of patients.

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The study reported that benefits of PCI were much greater in patients with severe angina. It included few patients who received stents. If stents had been used more frequently, outcomes might be more favorable in the PCI group.

I believe primary care clinicians should generally advise patients with severe and frequent angina to start optimal medical therapy immediately and to consult a cardiologist.

The primary care clinician’s approach to patients with angina requires keen clinical judgment in order to advise patients, and to work with the patient to determine his personal informed decision.

ANKLE BRACHIAL INDEX

May Improve The Accuracy Of Cardiovascular Risk Prediction Beyond The FRS.

7-3 ANKLE BRACHIAL INDEX COMBINED WITH FRAMINGHAM RISK SCORE TO PREDICT CARDIOVASCULAR EVENTS AND MORTALITY

Major cardiovascular and cerebrovascular events often occur in individuals without known preexisting cardiovascular disease. Prevention of these events starts with the accurate identification of those at risk. The
The Framingham risk score (FRS; risk of cardiovascular events over the following 10 years) is often considered the reference standard, but has limited accuracy. It tends to overestimate risk in low risk populations and underestimate risk in high risk populations. The FRS includes age, total cholesterol, high-density cholesterol, BP, diabetes, and smoking status.

The ankle/brachial index (ABI), the ratio between systolic BP in the ankle and systolic BP in the arm, is easily measured.

This study determined if the ABI provides information on risk independently of the FRS, and can improve risk prediction.

These investigators conducted a literature search which identified 16 population cohort studies fulfilling their inclusion criteria. All subjects were derived from a general population (over 48,000 individuals; men and women in equal numbers; mean age varied from 47 to 78).

A meta-analysis was conducted in individuals who had no previous history of coronary heart disease (CHD). All had ABI and FRS measured at baseline.

Determined hazard ratios (HRs) for ABI, subdivided into 10 categories compared to a reference ABI of 111/100 to 120/100

Median follow-up ranged from 3 to 17 years (most more than 10 years) to determine total cardiovascular mortality and morbidity.

The HRs for death for different levels of ABI compared with the reference (111/100 to 120/100) increased consistently for men and women with decreasing ABI:

- For 101-110/100 there was a slightly higher HR above reference.
- For each 10 mm lower ABI, HR rose steadily to 4 at < 60/100.

The prevalence of a low ABI increased with age.

The ABI provided independent risk information in addition to the FRS. A low ABI (<90/100) approximately doubled the risk of total mortality, cardiovascular mortality, and major cardiovascular events as predicted by the FRS.

In predicting the 10-year risk of total CHD, these results indicate that measurement of ABI would change the risk determined by the FRS alone in approximately 1 of 5 men.

Conclusion: Measurement of ABI may improve the accuracy of cardiovascular risk prediction beyond the FRS.

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I believe addition of other risk factors, easily determined in primary care, would improve prognosis more efficiently. These would include: BMI, family history, waist circumference, and possibly apolipoprotein B and apolipoprotein A. (See the following article.)

I believe addition of ABI would increase costs to the public, especially the Medicare program, with little benefit. Primary care’s challenge is to encourage patients to respond to the risk factors we already have instead of adding others.
Our efforts should be on prevention (eg, preventing the atherosclerotic disease which causes the decrease in ABI) rather than informing the patient that his ABI indicates disease already present.

**APOLIPOPROTEIN A AND B**

*The ApoB/ApoA Ratio Was The Most Powerful Marker Associated With MI. It Should Be Introduced Into Routine Clinical Practice.*

7-1 LIPIDS, LIPOPROTEINS, AND APO-LIPOPROTEINS AS RISK MARKERS OF MYOCARDIAL INFARCTION IN 52 COUNTRIES

“Perhaps no issue in lipodology has been as contentious as whether ApoB and ApoA are better markers than their cholesterol counterparts of risk of vascular disease.”

The American Diabetes Society and the American College of Cardiology have stated (2008) that ApoB is the test of choice to assess the adequacy of statin treatment, and should therefore be introduced into routine clinical practice.

This large case-control study included over 9000 cases of acute MI and over 12 000 controls—age and sex matched in 52 countries. It included all major ethnic groups. Non-fasting blood samples were available in all to determine levels of apo-lipoproteins and cholesterol. (ApoA and ApoB are unaffected by the non-fasting state, as are total cholesterol and HDL cholesterol.)

The investigators calculated odds ratios and population attributable risk (PAR) for acute MI for each measurement overall, and for each ethnic group.

Patients with MI had higher total cholesterol (T-c), non-HDL-cholesterol (non-HDL-c), and Apo B (the Bad guy) than controls.

With each decile increase in the ApoB/ApoA ratio, the risk of MI was greater than for each decile increase in the T-c/HDL-c ratio.

A one standard deviation (SD) difference in ApoA (the Advantageous guy) was associated with a 33% reduction in risk of MI, compared with a reduction of 15% for one SD of the T-c/HDL-c ratio.

The ApoB/ApoA ratio was the most powerful marker associated with MI in both sexes.

The overall PAR for acute MI for the ApoB/ApoA ratio was 54%; for the T-c/HDL-c ratio was 32% For comparison, the PAR for smoking was 44%

“In all ethnic groups, and both sexes, the ApoB/ApoA ratio was a better risk marker for myocardial infarction than was the ratio of total cholesterol/HDL cholesterol.”

The clinical measurement of apo-lipoproteins is standardized, simple, inexpensive, and can be done non-fasting. “Our data provide broad and straightforward support that ApoB and ApoA should be introduced into clinical practice for the assessment of risk of vascular disease.”

Conclusion: The non-fasting ApoB/ApoA ratio was superior to any of the cholesterol ratios in estimation of risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages.
ASPIRIN

No Benefit in The Primary Prevention Of Cardiovascular Events, Even in High Risk Groups.

11-9 ASPIRIN FOR PREVENTION OF CARDIOVASCULAR EVENTS: Is only effective in established cardiovascular disease.

The use of aspirin for the secondary prevention of cardiovascular events in patients with coronary or cerebrovascular disease is well established. A meta-analysis reported that aspirin was beneficial in patients with acute myocardial infarction (MI), ischemic stroke, unstable or stable angina, and those with previous MI, stroke, or cerebral ischemia. However, not all patients with cardiovascular disease benefit from aspirin as shown by a recent meta-analysis of aspirin trials in peripheral artery disease.

Studies evaluating the possible benefits of aspirin for the primary prevention of cardiovascular disease have consistently been negative. A review by the FDA in 2004 evaluated five primary prevention trials and found that they were all negative for their end-points. Further examination of trials in the higher risk subgroups (Framingham scores > 8-10% / decade) also failed to show a benefit of aspirin. The FDA did not extend the labeling of aspirin for primary prevention.

Despite the consistently negative evidence, some guidelines recommend aspirin to prevent cardiovascular events in subjects at higher risk who do not have existing cardiovascular disease, and in patients with diabetes. The assumption is that the positive findings of aspirin in patients with symptomatic coronary or cerebrovascular disease can be extrapolated to high-risk populations who have no clinical evidence of cardiovascular disease.

Risk assessment alone cannot predict which patients will benefit from aspirin. In fact, the only predictor of clinical benefit from aspirin is a history of major coronary or cerebral ischemic events. This is in sharp contrast to evidence that statin drugs and anti-hypertension drugs have clinical benefit that extends to all risk groups, including those with and without CVD. In these examples, the differences between primary and secondary prevention is the absolute reduction in risk. Primary prevention populations have a lower absolute risk, but receive the same relative risk reduction.

A total of 7 well controlled trials now show that aspirin has no benefit for primary prevention of cardiovascular events, even in people at high risk. Aspirin should be prescribed only in patients with established cardiovascular disease (secondary prevention).

See the following abstract for a contrary view.
The Role Of Antiplatelet Therapy For Primary Prevention In Individuals With Diabetes Remains To Be Elucidated.

11-10 ASPIRIN FOR PRIMARY PREVENTION OF CARDIOVASCULAR EVENTS IN DIABETES: Still an Open Question

This issue of JAMA presents a trial from Japan specifically designed to address the issue of antiplatelet therapy for primary prevention of cardiovascular events in patients with diabetes. It reported no benefit in reducing the risk of a composite endpoint of atherosclerotic events and mortality.

Aspirin was associated with an increased risk of gastrointestinal bleeding and retinal hemorrhage. Four patients in the aspirin group required blood transfusion.

Should this study be considered as definite proof that aspirin is less effective in patients with diabetes than in other high-risk groups? The editorialist believes the question is not settled. The trial poses some problems in terms of generalizability of results. There was a very low baseline risk of cardiovascular disease in the study groups.

“The role of antiplatelet therapy (for primary prevention) in the context of the overall approach to cardiovascular risk reduction in individuals with diabetes remains to be elucidated.”

How should the primary care clinician now respond? The decision to prescribe aspirin should be made on an individual patient basis after careful evaluation of the balance between the expected benefits and the risk of major bleeding.

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I believe low-dose aspirin still has a place in primary prevention of cardiovascular disease, in high risk patients including those with diabetes. It should be used in conjunction with reduction in all other risk factors. Used alone, the absolute benefit in reducing cardiovascular events will be very small, and the NNT will be very high.

The editorialists agree that low-dose aspirin is indicated in patients with established cardiovascular disease (a history of myocardial infarction or ischemic stroke).

Considered two patients age 60:

A has an acute MI. He had not previously received low dose aspirin. Now it is prescribed based on its putative effectiveness in secondary prevention. It will be continued indefinitely. Treatment results in improvement of dyslipidemia, BP, BMI and abdominal girth, and fitness. He stops smoking. Aspirin is likely to be continued despite his risk of a recurrent cardiovascular event being greatly reduced.

B has not experienced a MI. His risk factors are just as high as patient A at the time of his MI.
He is at high risk for a cardiovascular event. Aspirin is not prescribed because his clinician does not consider it indicated for primary prevention.

Benefits of aspirin will be very low in both patients, I believe risk is higher in B than in A. And aspirin may be beneficial in B. Some patients who have never experienced a cardiovascular event may be at higher risk than some who have experienced a myocardial infarction. Benefit of primary prevention may be as great as secondary prevention in select patients.

Low-dose prophylactic aspirin has become engrafted in our medical practice. I believe use will continue. Primary care clinicians should limit use to very high risk patients along with other more important interventions to reduce risk. Whether diabetes per se is a high enough risk factor is a matter of debate. Most patients with diabetes have other risk factors.

Long-term aspirin use depends on the individual choice of an informed patient. Individualization is key.

Fashions in medicine change. At times, doubt about well-accepted practices may begin to creep in regarding applications that have been generally accepted for years, and advised by guidelines.

ASTHMA

Long-Acting Beta-Agonists Have A Narrow Therapeutic Window. They Deserve Caution

7 -5 EFFECTS OF ADDING SALMETEROL TO INHALED CORTICOSTEROIDS ON SERIOUS ASTHMA-RELATED EVENTS.

Early guidelines recommended that all patients with persistent asthma receive regular treatment with inhaled corticosteroid. For patients whose asthma is not controlled, adding a long-acting beta-agonist was recommended.

Subsequently there has been conflicting evidence about safety of combined inhaled LABA + inhaled corticosteroids.

This study examined whether the incidence of severe asthma-related events (including hospitalizations, intubations, deaths, and severe exacerbations) differed in persons receiving inhaled salmeterol + inhaled corticosteroids vs inhaled corticosteroid alone. It included 66 randomized, controlled trials (over 26 000 patients with moderate to severe persistent asthma ) comparing inhaled corticosteroid + LABA (usually administered as twice-daily fluticasone/salmeterol (Advair; GlaxcoSmithKline), often by means of a single device), vs inhaled corticosteroid (Flovent; fluticasone; GSK) alone in patients with persistent asthma.

All trials were reported by GlaxcoSmithKline. Only 26 trials were longer than 12 weeks.

Severe asthma exacerbations requiring systemic corticosteroids:

- Combined therapy: 5%
- Inhaled corticosteroid alone: 8%

(Combined therapy prevented some severe exacerbations of severe asthma.)
Asthma-related hospitalizations (combined therapy vs corticosteroid alone) = 35 vs 34.
A subset of 24 trials showed a decreased risk of severe asthma-related exacerbations for combined therapy vs corticosteroid alone.

Few deaths and intubations limited the ability to measure risks for these outcomes. However, the number of asthma-related deaths has declined steadily since 1996 in the USA since salmeterol was introduced (1994) and then salmeterol + fluticasone became available in a single device (2001).

Conclusion: In patients with persistent asthma, salmeterol combined with inhaled corticosteroid may reduce the risk of severe asthma exacerbations, as compared with corticosteroids alone. The combination does not alter the risk of asthma-related hospitalizations, and may not affect the risk for asthma-related deaths or asthma-related intubations.

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Regrettably, when we read about trials supported and reported by large drug companies we almost automatically look for bias. I believe the authors of this study took great pains to avoid the appearance of bias.

The message for primary care:

1) Try inhaled corticosteroids first.
2) If not effective, add a inhaled LABA
3) Do not use inhaled LABA alone as first-line therapy.
4) If combination therapy fails, high dose oral or parenteral corticosteroids may be required.

Would it be appropriate to prescribe a short-term of high dose oral corticosteroid for select patients with persistent, troublesome asthma? This could be held in reserve and be taken immediately when experiencing a severe exacerbation, as a bridge until the patient could access emergency treatment.

BEREAVEMENT

Associated With Less Aggressive Medical Care And Earlier Referral To Hospice

10-3 ASSOCIATIONS BETWEEN END-OF-LIFE DISCUSSIONS, PATIENT MENTAL HEALTH, MEDICAL CARE NEAR DEATH, AND CAREGIVER BEREAVEMENT ADJUSTMENT.

End-of-life discussions (EOLD) offer patients the opportunity to define their goals and expectations for the medical care they want to receive near death. These discussions mean confronting the limitations of medical treatments and the reality that life is finite, both of which may cause psychological distress. Talking about death can be difficult.

This study examined the associations between EOLD and the medical care terminally ill cancer patients receive. (Patients with advanced cancer who prefer life-extending therapy are often overly
optimistic about their chances of survival.) Do EOLD benefit or harm? Do they lead to fewer aggressive interventions?

The study (2002-08) included 332 patients who died of incurable cancer. It examined the medical care they received in the final week of life, and assessed caregiver’s quality-of-life (QOL) at a median of 6 months later, at a point that they would likely be beyond acute grief.

At a baseline interview patients were asked “Have you and your doctor discussed any particular wishes you have about care you want to receive if you were dying?”

EOLD were not associated with patients being depressed, sad, or worried. Patients who engaged in the discussion were more likely:

- To accept that their illness was terminal
- To prefer treatment focused on pain and discomfort over life-extending treatment
- To have completed a do-not-resuscitate order
- To receive fewer aggressive interventions
- To be enrolled in hospice for more than a week
- Were less likely to receive ventilation, undergo resuscitation, and to be admitted to intensive care

Bereavement outcomes:

A direct relationship existed between patients’ QOL near death and their bereaved caregivers’ QOL

Caregivers of patients with high QOL felt better prepared for the death and experienced less regret at follow-up

Caregivers of patients who received aggressive care:

- Were at higher risk of developing a major depressive disorder
- Were at higher risk of feeling unprepared for the patient’s death
- Experienced worse QOL, more regrets, and were at higher risk of developing a major depressive disorder 6 months later

QOL improved the longer the patient was enrolled in hospice. Patients who received less than a week of hospice care had the same QOL scores as patients who received no hospice care, suggesting that patients benefit more from early hospice referral.

The association between EOLD and patients’ preferences for less aggressive care is noteworthy. EOLD may make patients more realistic about benefits of aggressive therapies.

By acknowledging that death is near, patients, caregivers, and physicians can focus on clarifying patients’ priorities and improving pain and symptom management.
Conclusion: End-of-life discussions are associated with less aggressive medical care and earlier hospice referrals. Aggressive care is associated with worse quality-of-life and worse bereavement adjustment.

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I believe this article will be helpful to many primary care clinicians and their patients. Compared with the past, more terminally ill patients accept death as a normal part of life. Death at an advanced age is not the taboo it once was. Death at an early age may be much more distressing. The goal is to lengthen the period of good quality of life and compress the period of bad quality.

To some, dying may be a time of reflection, forgiveness, and acceptance.

There are, however, cultural differences which clinicians should be aware of. The article noted that many participants were of ethnic minorities.

Many clinicians may find it difficult to talk to individual patients about impending death. And have difficulty in broaching the subject. The closer the patient-physician relationship, the easier the conversation will become.

A simple question “Are you at peace” may be an introduction.

CALCIUM SUPPLEMENTATION

1200 Mg Of Calcium Daily Had Beneficial Effects On BMD; 600 Mg Did Not

11-3 RANDOMIZED, CONTROLLED TRIAL OF CALCIUM SUPPLEMENTATION IN HEALTHY, NON-OSTEOPOROTIC, OLDER MEN

Calcium supplementation is widely regarded as a fundamental component of the prevention and treatment of postmenopausal osteoporosis in women. It has been assumed that calcium plays a similar role in men who have osteoporosis. The US Surgeon General recommends increases in calcium intake across the entire population, including men.

There has been no consistent evidence, however, that calcium supplements affects bone mineral density (BMD) in men.

This double-blind, randomized, controlled trial followed 323 healthy men (mean age 57) for 2 years. Randomized to: 1) placebo; 2) 600 mg calcium daily; 3) 1200 mg calcium daily [600mg twice daily]. None received vitamin D supplements.

At baseline (means):
- Calcium intake 850 mg/d
- Serum 25-OH vitamin D 37 ng/mL (SI reference = 18-36)
Bone density T score

<table>
<thead>
<tr>
<th>Location</th>
<th>Score</th>
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<tbody>
<tr>
<td>Lumbar spine</td>
<td>+0.2</td>
</tr>
<tr>
<td>Hip</td>
<td>-0.2 (Not osteopenic or osteoporotic.)</td>
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Over 2 years, BMD increased at all sites in the group receiving 1200 mg/d by 1% to 1.5% compared with placebo. Lumbar spine BMD increased by 1.2% in the first 6 months, followed by a more gradual increase over the 2 years to 1.5%. BMD in those receiving 600 mg did not differ from placebo.

“The present data establish that 1.2 g of calcium given in a divided dose produces substantial benefit to BMD throughout the skeleton in vitamin-D-sufficient men.”

Conclusion: Calcium, 1200 mg/d had beneficial effects on BMD in men comparable with those found in postmenopausal women; 600 mg /d was ineffective.

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The problem of osteopenia and osteoporosis in older men is becoming more publicized. Vitamin D and calcium supplements are as necessary as in women.

Auckland, the site of the study, is a northern city in NZ, closer to the equator. Its latitude is 37° south, a sunny climate. I doubt that the oral intake of vitamin D is any greater than any other city. Perhaps the sunlight maintained serum levels of 25-OH D.

Note that the mean dietary intake of calcium was 850 mg. When 1200 mg is added, the total grows to over 2000 mg. A two-year period is not long enough to detect adverse effects of this total intake.

The rapidity of increase in BMD surprised me.

CERVICAL CANCER

Women with A Negative HPV Test May Safely Be Screened Every 6 Years.

10-2 LONG TERM PREDICTIVE VALUES OF CYTOLOGY AND HUMAN PAPILLOMAVIRUS TESTING IN CERVICAL CANCER SCREENING

Seven primary screening studies included over 24 000 women. All routinely used both cytology and HPV tests. Included only women with adequate cytology and HPV tests at baseline, and with at least one follow-up cytological test. Cytology tests in Europe are commonly recommended every 3 years.

Regarded abnormal cytology as the equivalent of atypical squamous cells of uncertain significance or worse.

Of the original 24 295 women, 381 developed confirmed cervical cancer during 6 years of follow-up.
Cumulative incidence of cervical cancer at 6 years (per 10 000 subjects):

<table>
<thead>
<tr>
<th>HPV status</th>
<th>Cytology status</th>
<th>Incidence (per 10 000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HPV + / cytology +</td>
<td></td>
<td>34</td>
</tr>
<tr>
<td>HPV + / cytology -</td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>HPV - / cytology +</td>
<td></td>
<td>2.7 (ten patients)</td>
</tr>
<tr>
<td>HPV - / cytology -</td>
<td></td>
<td>0.27 (one patient)</td>
</tr>
</tbody>
</table>

The cumulative incidence of cancer in those HPV + rose continuously over 6 years. The cumulative rate of cancer in those positive for cytology & negative for HPV remained below 3%.

In patients negative for both tests, the cumulative incidence rate of future cancer during 6 years of follow-up was uniformly low. Double negativity confers a long lasting protective effect.

Conclusion: The consistently low 6-year cumulative incidence rate of cervical cancer among women with a negative HPV test suggests that screening intervals for HPV could safely be lengthened to 6 years. This could at least partially compensate for the increased referral rate resulting from the higher false positive rates of HPV-based screening strategies, especially in younger women.

Both cervical intraepithelial neoplasia (CIN) and HPV can regress. The latter due to development of immunity, especially in younger women.

I believe both tests should be done simultaneously. Note that if both are positive, the rate of progression to cancer over 6 years was about 3 out of 1000.

The tests are more predictive in older women.

**COLON CANCER**

*Currently Imperfect, But Promising*

**10-10 STOOL DNA AND COLON CANCER PREVENTION**

Historically, screening approaches have sought to detect established colo-rectal cancer. The identification of precancerous adenomatous polyps is clearly preferable.

Guidelines now emphasize detection of precancerous polyps as the most effective strategy to prevent death from CRC. Colonoscopy is recommended. Testing for occult blood in the stool is notoriously insensitive.

The adenoma-to-carcinoma sequence in colon cancer is based on the stepwise progression of specific genetic alterations that parallel the histopathologic progression from pre-neoplasia to neoplasia. Detection of gene mutations in tumor cells sloughed off into stool is possible. Two DNA tests are available—Stool DNA Test-1 (SDT-1) and more recently SDT-2. The latter assay includes 3 genes which are classically mutated at the stage of precancerous adenomas.
SDT-2 is much more promising—46% of screen relevant neoplasms had a positive result. (Sensitivity = 46%) This would miss more than half of screen-relevant neoplasms. There are many false positives—16% to 26% of those tested positive did not have a neoplasm. Such high false positive rates would be problematic for population-wide screening.

For those unwilling to have a screening colonoscopy, a stool DNA could provide a noninvasive option that is superior to conventional occult blood testing.

----------

I believe, at present, there is no substitute for optical colonoscopy.

COLON POLYPS

**Large Polyps Occur In About One In 14 Asymptomatic Patients Over Age 50. Most Are Precancerous.**

**9-5 PREVALENCE OF COLON POLYPS DETECTED BY COLONOSCOPY SCREENING IN ASYMPTOMATIC BLACK AND WHITE PATIENTS**

This study prospectively collected from over 80,000 whites and over 5000 blacks who received an initial screening colonoscopy. All were asymptomatic.

Main outcome measures = prevalence and location of polyps 10 mm and over, adjusted for age, sex, and family history of colon cancer.

About 84% of polyps of this size were advanced adenomas: tubular adenoma, serrated adenoma, adenoma with villous histology, high grade dysplasia, or invasive cancer. (Only 10% to 20% of polyps ≥10 mm are not neoplastic.)

Prevalence of one or more polyps ≥10 mm:

<table>
<thead>
<tr>
<th></th>
<th>White (%)</th>
<th>Black (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>6.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Male</td>
<td>7.7</td>
<td>8.4</td>
</tr>
<tr>
<td>Female</td>
<td>4.7</td>
<td>7.2</td>
</tr>
</tbody>
</table>

Prevalence of one or more polyps ≥10 mm according to age:

<table>
<thead>
<tr>
<th>Age Group</th>
<th>White (%)</th>
<th>Black (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50</td>
<td>4.2</td>
<td>6.2</td>
</tr>
<tr>
<td>50-59</td>
<td>5.3</td>
<td>6.1</td>
</tr>
<tr>
<td>60-69</td>
<td>7.1</td>
<td>10.5</td>
</tr>
<tr>
<td>70-79</td>
<td>7.7</td>
<td>10.8</td>
</tr>
</tbody>
</table>

*(Note the increase in prevalence beginning at age 60.)*

Conclusion: Asymptomatic black patients were more likely than whites to have polyps ≥10 mm.
Polyps ≥10 mm were more common after age 60.
The great majority of polyps ≥10 mm were neoplastic (pre-cancer).

---

I abstracted this article, not because of the modest racial difference, but to inform that larger polyps occur in about one in 14 asymptomatic patients over age 50. Most are precancerous. Removing these polyps will reduce incidence of CRC and death from CRC.

**COLONOSCOPY**

*These Findings Provide Support For Rescreening After An Interval Of 5 Years Or Longer*

9-6  **FIVE-YEAR RISK OF COLORECTAL NEOPLASIA AFTER NEGATIVE SCREENING COLONOSCOPY**

This study determined the incidence of any neoplasia and advanced neoplasia at a 5-year rescreening interval among patients (2943) who had no neoplasia on the initial colonoscopy.

Forty two % (1243) returned for rescreening at 5 years. Of these, 199 had hyperplastic polyps at baseline. These were considered to have had negative colonoscopies.

At 5 years, categorized patients according to the most advanced lesion present: no polyp; hyperplastic polyp; tubular adenoma less than 1 cm; advanced adenomas (tubular adenoma one or more cm in diameter, a polyp with villous histological features or high grade dysplasia); or a colorectal cancer [CRC]).

No CRCs were detected on the rescreen.

Outcomes from a 5-year repeat colonoscopy:

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of subjects</th>
<th>Any adenoma (%)</th>
<th>Advanced adenoma (%)*</th>
<th>NNS**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1256</td>
<td>16</td>
<td>1.3</td>
<td>79</td>
</tr>
<tr>
<td>Men***</td>
<td>712</td>
<td>20</td>
<td>1.8</td>
<td>55</td>
</tr>
<tr>
<td>Women</td>
<td>544</td>
<td>10</td>
<td>0.6</td>
<td>182</td>
</tr>
<tr>
<td>Hyperplastic ****</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>polyp a baseline</td>
<td>199</td>
<td>24</td>
<td>2.0</td>
<td>50</td>
</tr>
<tr>
<td>No polyps at</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>1057</td>
<td>15</td>
<td>1.1</td>
<td>88</td>
</tr>
</tbody>
</table>

(* Almost all were villous.)

(** Number needed to screen at 5 years to detect one advanced adenoma.)

(**** Adenomas and advanced adenomas were more common in men.)

(**** Hyperplastic polyps may be an independent risk factor for adenoma and advanced adenoma.)
The natural history of advanced adenomas is not known. There is uncertainty about the clinical importance of “advanced adenoma” and its appropriateness as a target for programs of screening and surveillance.

“Given the low risk of advanced neoplasia, we believe that 5 years is probably the minimum duration of protection for nearly all persons who do not have a family history of colorectal cancer.”

Conclusion: Among persons previously screened with colonoscopy who have no neoplasia, the 5-year risk of CRC is extremely low. The risk of advanced neoplasia is also low. It is lower for women than for men. These findings suggest that among persons at average risk for CRC, rescreening colonoscopy need not be performed sooner than 5 years after an initial negative colonoscopy.

I believe this has practical implications for advice given to patients by primary care clinicians.

Colonoscopies may be performed too frequently. Costs and inconvenience are high. Complications occur in up to 2 in 1000 patients. But, there is no doubt that colonoscopy saves lives.

The study does not try to answer remaining questions:

1) How frequently to rescreen those with a polyp at the initial screen?
2) At what interval should we advise an individual patient with a negative screen to be rescreened?
3) Should patients with a hyperplastic polyp be screened more frequently? Should men be screened more frequently than women?
4) How to factor in costs, inconvenience, and possible adverse effects of colonoscopy?
5) How often to screen patients with a positive family history?

This is a good example of the value of negotiations between physicians and individual patients based on informed consent. Some will wish early rescreen; some will be comfortable to extend the period. Some will never return.

CORONARY ARTERY (HEART) DISEASE

“This Should Serve As Encouraging News To Patients With Coronary Disease.”

8-9 FINDING THE COURAGE TO RECONSIDER MEDICAL THERAPY FOR STABLE ANGINA

Coronary stents have revolutionized percutaneous coronary intervention (PCI) and have reduced the rate of complications and the need for repeat interventions. Clinician’s thresholds for PCI intervention have been markedly altered. Now, the presence of any angina can precipitate coronary angiography to detect amenable lesions, followed by PCI. Symptoms are no longer a prerequisite. Aggressive strategies for screening may reveal lesions that can be treated with PCI.
The therapeutic paradigm has reversed, with medical therapy generally reserved for those who have exhausted revascularization options.

The trial showed that, with contemporary medical treatment, the majority of patients had substantial improvements in health status that were sustained for several years. The rapid improvement with optimal medical therapy alone suggests that anginal medications are underused.

This underscores a major challenge to clinicians—how to successfully execute a strategy of optimal medical therapy in a health care system that provides strong financial rewards for PCI but few rewards for careful management of medications.

A very reasonable take home message from the trial is to pursue optimal medical therapy initially, and if it is ineffective, turn to PCI. Executing such a strategy will require “courage” to reconsider the algorithms of current care and the changes in policy that are necessary to give appropriate value to the effort that is required to manage medications optimally, and to monitor the health status of patients.

----------

The study reported that benefits of PCI were much greater in patients with severe angina. It included few patients who received stents. If stents had been used more frequently, outcomes might be more favorable in the PCI group.

I believe primary care clinicians should generally advise patients with severe and frequent angina to start optimal medical therapy immediately and to consult a cardiologist.

The primary care clinician’s approach to patients with angina requires keen clinical judgment in order to advise patients, and to work with the patient to determine his personal informed decision.

“Risks Are Systematically Underestimated Among Persons With Lower SES”

12-4 SOCIOECONOMIC STATUS AND CORONARY HEART DISEASE PREDICTION

Disparity in life expectancy between groups of individuals with low social economic status (SES) and those with high SES has been increasing. Much of this disparity is attributable to higher mortality from coronary heart disease among persons with lower SES.

Disparities arise because of: early life environment; material disadvantage; social and behavioral risk factors; access to care; costs; and health literacy.

The risk of low SES for CHD is independent of age, sex, diabetes, physical activity, diet, cholesterol, and bodyweight.

A study from Scotland reported that the Framingham risk score (FRS) underpredicted risk of CHD among persons with low SES. Predicted by the FRS, individuals living in communities with the lowest income had a 3% higher estimated risk than those living in the wealthiest communities. Actually, the risk was 41% higher.

----------
Primary care clinicians deal with individuals. How do we measure the SES of an individual? I have followed the “Polypill” concept for years. The original recommendation was to give the pill to everyone over age 50. Limiting the pill to individuals with low SES might be more effective.

**Screen Patients with CHD for Depression**

12-5 ROUTINE DEPRESSION SCREENING ADVISED FOR PATIENT WITH CORONARY HEART DISEASE

Up to 20% of patients with myocardial infarction (MI) meet the criteria for major depression. Depression is not a “normal” occurrence after a MI.

The American Heart Association advises clinicians to regularly screen patients with CHD for depression. The American Psychiatric Association agrees.

Comorbidity of depression and CHD leads to worse outcomes for both conditions. Treatment includes cognitive-behavior therapy and physical activity. SSRIs such as sertraline (Generic; Zoloft, Pfizer) and citalopram (Generic; Celexa, Forest) seem safe soon after an MI.

There is evidence that patients who do not get better from their depression are at high risk of dying.

**C- REACTIVE PROTEIN** (See STATIN DRUGS [11-2] )

**DIABETES**

*An Unrecognized Complication Of Diabetes. May Be Stronger Among Younger Persons With Diabetes.*

7-6 DIABETES AND HEARING IMPAIRMENT

The present study used recent national survey data to examine the relationship between diabetes and hearing impairment. The NHANES (National Health and Nutrition Examination Study) 1999-2004 included over 5000 persons who completed an audiometric examination and diabetes questionnaire.

Pure tone air conduction thresholds were obtained for each ear at frequent frequencies (500 Hz or less were considered low frequency; 1000 to 2000 Hz mid-range frequency; and tones over 3000 Hz were considered high frequency.

Prevalence of hearing impairment (hearing loss [HL]) in the worse ear:

<table>
<thead>
<tr>
<th></th>
<th>Diabetes (%)</th>
<th>No Diabetes (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild or greater severity (&gt; 25 dB HL)</td>
<td>21</td>
<td>9</td>
</tr>
</tbody>
</table>
Prevalence (%) of low or mid-frequency hearing impairment of greater severity according to age:

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Diabetes</th>
<th>No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-49</td>
<td>16</td>
<td>5</td>
</tr>
<tr>
<td>50-59</td>
<td>32</td>
<td>14</td>
</tr>
<tr>
<td>60-69</td>
<td>36</td>
<td>30</td>
</tr>
</tbody>
</table>

“We estimate a prevalence of low- or mid-frequency hearing impairment of mild or greater severity of 28% among people with diabetes.” Proportionally, loss is greater in persons under age 60.

Conclusion: Hearing impairment may be an unrecognized complication of diabetes, especially in younger persons. Diabetes seems to be an independent risk factor. Screening for hearing loss among persons with diabetes may be justified.

This is my first encounter with this relationship.

That hearing loss in more common in younger persons is an important clinical point. Younger persons may not recognize their hearing loss.

The question remains—will tighter control at an earlier age prevent hearing loss?

**Metformin Moderately Protective; Rosiglitazone Possibly Harmful.**

**10-5 CARDIOVASCULAR OUTCOMES IN TRIALS OF ORAL DIABETES MEDICATIONS**

Improvements in control of glucose levels have been shown to reduce incidence of microvascular disease. The effect on long-term cardiovascular (macrovascular) complications is not clear.

This literature search found 40 randomized controlled trials that reported macrovascular outcomes and mortality associated with second-generation sulfonylureas, biguanides, thiazolidinediones, and meglitinides for treatment of type-2 diabetes (DM-2).

Risk of fatal and non-fatal cardiovascular disease (CVD) and all-cause mortality:

A. Metformin vs placebo or other oral agents for cardiovascular mortality (7 trials)
   
   Overall pooled odds ratio = 0.85 favoring metformin. (CI = 0.68-1.05)

B. Any sulfonylurea vs placebo or other oral agent (5 trials)
   
   Overall pooled odds ratio = 0.89 favoring sulfonylurea (CI = 0.69-1.11)

C. Rosiglitazone vs placebo or other oral agents (5 trials)
   
   Overall pooled odds ratio = 1.69 favoring placebo or other agents (CI = 0.51-6.11)

D. Pioglitazone vs placebo or other oral agents (6 trials)
Overall pooled odds ratio = 0.86 favoring pioglitazone (CI = 0.78-1.00)

Metformin was the only drug associated with a significant decrease in mortality. Rosiglitazone was the only drug associated with a possible increase in risk of cardiovascular morbidity or mortality.

“The poor quality and inconsistent reporting of adverse events and the profound lack of long-term studies make it difficult to draw firm conclusions.” The reduction observed when intensive control was compared with conventional treatment suggests that glycemic control per se may be partially driving cardiovascular risk reduction.

Conclusion: Compared with other oral agents, metformin appears moderately protective against cardiovascular effects. Rosiglitazone is possibly harmful.

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Epidemiological studies have reported a linear relationship between HbA1c and risk of CVD in type-2 diabetes. It would seem reasonable that reductions in HbA1c would reduce risk. Despite many trials, the association has not been established. There is a glimmer of hope from metformin.

Two recent trials of oral drugs reported no benefit, and possible harm.

We await information about effects of the incretin drugs and insulin.

Primary care clinicians can reassure patients that reducing HbA1c as much as possible, determined by individual ability to comply with a defined drug regimen and incidence of hypoglycemia, will reduce risk of microvascular complications. The American College of Physicians Guidelines (Annals Int Med September 18, 2007; 147: 417-22) recommends:

To prevent microvascular complications of diabetes, the goal for glycemic control should be as low as feasible without undue risk for adverse effects, or an unacceptable burden on patients. Treatment goals should be based on a discussion of the benefits and harms of specific levels of glycemic control with the patient. A HbA1c level less than 7%, on individualized assessment, is a reasonable goal for many, but not all patients.

Protection against CVD complications of DM-1 depends much more on standard risk-lowering intervention (lipid, BP, and weight control; smoking cessation; and maintaining physical fitness) than on control of HbA1c.

Increases In Levels Of Insulin, Not Glucose, May Be Etiologic

10-6 GLUCOSE LOWERING TO CONTROL MACROVASCULAR DISEASE IN TYPE-2 DIABETES

Whether reduction of cardiovascular risk results from intensive glycemic control in
DM-2 remains an unanswered hypothesis. A recent large trial of intensive treatment of DM-2 was stopped early because of an increase in total mortality. Other trials have failed to provide evidence that intensive glucose control leads to cardiovascular protection.

Numerous trials have demonstrated that high levels of HbA1c and glucose are predictors of cardiovascular disease. The relationship of glucose levels to cardiovascular disease mortality is especially strong in patients with established cardiovascular disease.

This may be explained by insulin resistance or hyperinsulinemia. In large population-based studies, insulin levels predict increased cardiovascular risk. High fasting insulin concentrations have been reported to be an independent predictor of ischemic heart disease. This raises the possibility that increases in levels of insulin, not glucose, may be etiologic in cardiovascular disease. Insulin has mitogenic effects on vascular smooth muscle and increases activity of plasminogen activator inhibitor, thereby decreasing fibrinolytic activity.

“If insulin levels are toxic to the cardiovascular system, then treatments designed to reduce insulin levels, rather than glucose levels, might be associated with a reduced risk of cardiovascular events in patients with type-2 diabetes.”

“It may be appropriate to focus on the aggressive control of insulin levels or insulin resistance rather than only on aggressive control of glucose levels.”

To my knowledge, only metformin and lifestyle interventions decrease insulin levels. The large trial mentioned is the ACCORD trial (Action to Control Cardiovascular Risk in Diabetes” (NEJM 2008; 358: 2560-72). Over 90% of participants were receiving rosiglitazone. This drug may have caused some of the adverse cardiovascular events.

I abstracted this article because it is provocative. I will look for further studies regarding possible toxicity of insulin.

---

Similar Glycemic Control Occurred With NPL or IG When Added To Oral Regimens

10-7 ADDITION OF NEUTRAL PROTAMINE INSULIN LISPRO OR INSULIN GLARGINE TO ORAL TYPE-2 DIABETES REGIMENS FOR PATIENTS WITH SUBOPTIMAL GLYCEMIC CONTROL

Glycemic control, preferably to HbA1c levels less than 7%, can substantially reduce the risk of microvascular, and possibly macrovascular complications in patients with type-2 diabetes (DM-2). Maintaining such levels is now recommended for clinical practice, but it is difficult to achieve despite escalating doses of oral drugs.
Most patients with DM-2 eventually require insulin added to oral agents as glycemic control becomes suboptimal. A single bedtime injection of a long-acting insulin added to oral agents is then the preferred treatment worldwide.

This study compared the clinical efficacy and safety of bedtime neutral protamine lispro (NPL) and insulin glargine (IG) added to ongoing oral therapy with stable doses of metformin and sulfonylureas in patients with DM-2. All had suboptimal control.

Randomized to 10 IU of NPL or IG at bedtime. Adjusted dose of insulin to target fasting glucose less than 100 mg/dL. Oral agents were continued at the pre-study doses. But, only metformin was permitted at the evening meal in order to minimize risk of sulfonylurea-induced nocturnal hypoglycemia.

HbA1c improved equally in both groups (-1.8%), reaching a plateau after 12 to 24 weeks.

Secondary outcomes did not differ between groups: HbA1c levels below 7% (62%); fasting plasma glucose < 100 mg/dL (40%); insulin dose; and body weight.

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>NPL</th>
<th>IG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hypoglycemic event</td>
<td>74%</td>
<td>67%</td>
</tr>
<tr>
<td>Symptomatic hypoglycemia</td>
<td>45%</td>
<td>40%</td>
</tr>
<tr>
<td>Nocturnal hypoglycemia</td>
<td>33%</td>
<td>25%</td>
</tr>
<tr>
<td>Severe hypoglycemia</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

“The results of our study confirm the feasibility of adding basal insulin to oral antihyperglycemic drugs, with intensive dose titration as a strategy for achieving recommended glycemic targets in patients with poorly controlled type-2 diabetes.”

Conclusion: Bedtime IG or NPL added to oral medication in patients with poorly controlled DM-2 resulted in similar glycemic control.

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The study reports surrogate outcomes—no clinical outcomes.

Poor control of DM-2 is a risk factor for micro-vascular disease. The relation with macro-vascular disease is less clear. Is an increased risk of hypoglycemia worth an indefinite lowering of risk of macro-vascular complications? Some recent trials have reported an increase in cardiovascular disease related to intensive glycemic control, possibly due to insulin toxicity. Only metformin and life-style interventions will improve glycemia without increasing insulin levels.

The usual methods of lowering macro-vascular risk (lipid, BP, and weight control, exercise, and possibly low dose aspirin) would likely lower risk much more than strict control of HbA1c.
A Legacy Effect

10-8  10-YEAR FOLLOW-UP OF INTENSIVE GLUCOSE CONTROL IN TYPE-2 DIABETES.

The original United Kingdom Prospective Diabetes Study (UKPDS) enrolled patients from 1977 to 1991, and was reported in 1998. At baseline, over 4200 patients with newly diagnosed type-2 diabetes (DM-2) were randomized to: 1) dietary restriction, or 2) intensive therapy with sulfonylurea, or insulin, or to metformin (in overweight patients). It reported that patients who received intensive sulfonylurea-insulin therapy had a lower relative risk of micro-vascular complications than did those receiving conventional dietary therapy, and a non-significant reduction of 16% in myocardial infarction (MI). In overweight patients who primarily took metformin, the relative risk of MI was reduced by a statistically significant 39%, and risk of death from any cause was reduced by 36%.

This post-trial study monitored over 3200 of the UKPDS patients for an additional 10 years (1998–2007). No attempt was made to maintain their previously assigned therapy. Examined clinical outcomes on an intention-to-treat basis, according to the previous randomization categories.

Between-group differences in HbA1c were lost after the first post-trial year.

In the sulfonylurea-insulin groups, during the post-trial period, as compared with dietary restriction, statistically significant relative risk reductions persisted for any diabetes-related end point (9%); diabetes-related death (17%); myocardial infarction (15%); death from any cause (13%); and microvascular disease (24%), There were no significant risk reductions in stroke or peripheral vascular disease.

In the metformin group, as compared with the dietary restriction, statistically significant relative risk reductions persisted for any diabetes-related end point (21%), diabetes-related death (30%); MI (33%), and death from any cause (27%). There were no significant reductions in microvascular disease, stroke, or peripheral vascular disease.

Conclusion: Despite early loss of differences in HbA1c, a continued reduction in microvascular risk and myocardial infarction and death from any cause was observed during 10-years of post-trial follow-up.

----------

Metformin (given to overweight patients) was superior to both sulfonylurea and insulin in reducing risk of any diabetes-related endpoint, diabetes-related death, myocardial infarction, and death from any cause during the period of the original trial and for 10 years thereafter.

Fortunately we have many more effective interventions to lower risk of cardiovascular disease than reduction in HbA1c. Since DM-2 is a strong risk factor, all patients with DM-2 should receive them.

Sulfonylurea-insulin was superior in reducing relative risk of microvascular disease.
If metformin reduced HbA1c levels over the years, why was microvascular disease not lowered? Would the benefits be even greater if the reductions in HbA1c levels had been continued during 1998-2007?

Regarding micro-vascular complications: The association between poor glycemic control and risk of microvascular complications (neuropathy, retinopathy, and diabetic kidney disease) is well established.

Regarding macro-vascular complication: Good glycemic control does reduce risk to some extent. There are also other interventions which reduce risk of vascular complications to a greater extent (lipid control, BP control, low-dose aspirin, physical fitness, and weight control).

I believe the latter interventions will reduce vascular complications to a greater extent than good glycemic control, with fewer adverse effects and increased patient-compliance and satisfaction. We should cautiously control glucose levels as well as possible while avoiding the adverse effect of hypoglycemia.

A Promising Treatment Option

10-9 EXENATIDE ONCE WEEKLY VERSUS TWICE DAILY FOR THE TREATMENT OF TYPE-2 DIABETES

Incretins are hormones normally produced by the upper gastrointestinal tract after eating, even before the blood glucose rises. They have multiple glucoregulatory effects: enhancement of glucose-dependent insulin secretion, reduction of glucagon secretion, reduction of food intake, and slowing of gastric emptying. As a result, plasma glucose levels are reduced.

Glucagon-like-peptide-1 (GLP-1) fulfills the criteria for an incretin. It is rapidly inactivated by a peptidase. It is not clinically useful. It must be administered by continuous subcutaneous infusion.

Exenatide is a GLP-1 analogue (an incretin mimetic), a 39-amino-acid peptide bearing a 50% amino-acid homology to GLP-1. It displays biological properties similar to human GLP-1. Its half life is over 2 hours. It is produced by chemical synthesis.

Exenatide significantly improves glycemic control in patients suboptimally controlled by commonly used oral agents including metformin, sulfonylureas, and thiazolidinediones. The exenatide currently available requires twice daily subcutaneous injections. It does not provide continuous activation of receptors.

A long-acting form of exenatide has been developed for once-weekly injection. The sustained-release formulation (SRF-exenatide; SRFE) consists of microspheres of exenatide combined with a
common biodegradable medical polymer, which has established use in absorbable sutures and extended release pharmaceuticals. This allows gradual drug delivery in a controlled rate.

This study compared safety and efficacy of the SRFE given once-weekly with that of the older preparation given twice daily in patients with DM-2.

All patients were receiving metformin, a sulfonylurea, a thiazolidinedione, or any combination of two of these, or were naïve to oral drugs. Oral drugs were continued.

<table>
<thead>
<tr>
<th>Outcomes at 30 weeks (mean;)</th>
<th>SRFE</th>
<th>Twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reductions in HbA1c</td>
<td>1.9%</td>
<td>1.5%</td>
</tr>
<tr>
<td>HbA1c 7% or less</td>
<td>77%</td>
<td>61%</td>
</tr>
<tr>
<td>Fasting glucose mg/dL</td>
<td>- 41 mg/dL</td>
<td>- 25 mg/dL</td>
</tr>
<tr>
<td>Weight loss</td>
<td>- 3.6%</td>
<td>- 3.7%</td>
</tr>
</tbody>
</table>

Postprandial plasma glucose and glucagon levels were lower in the SRFE group.

Adverse effects:

- Nausea was common (34%); vomiting (18%), predominantly mild.
- No episodes on major hypoglycemia, irrespective of background sulfonylurea use.
- Withdrawals due to adverse events were 6.1% for once weekly and 4.8% for twice daily.

Conclusion: Exenatide once-weekly resulted in greater improvements in glycemic control than exenatide given twice daily, with no increase in risk of hypoglycemia and with similar reductions in body weight.

This is not a practical point at this time. SRFE is not yet available. I abstracted the article because SRFE may be a significant advance.

If the preparation becomes available, I believe primary care clinicians should abide by the general rule for new drugs and wait a few years to be assured of adverse effects before prescribing it.

The Health Of The Mouth Can Have Significant Effects On The Health Of The Rest Of The Body

12-6 ORAL HEALTH—DIABETES LINK

Poor oral health can have significant effects on the health of the rest of the body.

When bacteria from periodontal disease (PD) are released into the blood stream, production of pro-inflammatory cytokines increases. The body’s response is systemic.

The link between PD and heart disease is one of the most commonly known associations.

Conditions within the oral cavity appear to have a particularly close relationship with diabetes.
Poor oral health may have adverse effects on diabetes.

The relationship goes both ways. Diabetes can lead to adverse changes in oral health.

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Although short and anecdotal, I believe this report calls attention to a relationship important to primary care.

Throughout the years, I paid scant attention to oral health of my patients. I assumed that it was entirely a dental problem.

**Resulted In A Moderately Lower Hba1c Level.**

**12-8 EFFECT OF A LOW-GLYCEMIC INDEX OR A HIGH-CEREAL FIBER DIET ON TYPE 2 DIABETES**

The relevance and practicality of applying the low-glycemic index diet (L-GID) to treatment of diabetes has been questioned. This randomized trial assessed the effect of a L-GID in patients with DM-2 treated with oral agents.

The trial entered 210 volunteer patients with DM-2 (mean age = 61). All were taking oral antidiabetes drugs (other than acarbose). The drugs were continued. HbA1c ranged between 6.5% and 8.0%. (Mean = 7.1%)

Randomized to: 1) L-GID, or 2) high-cereal fiber diet as a control. The diets were structured.

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<tr>
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<th>Baseline</th>
<th>6 months</th>
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<tbody>
<tr>
<td></td>
<td>High fiber</td>
<td>L-GID</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.07</td>
<td>7.14</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>141</td>
<td>139</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>87.8</td>
<td>87.0</td>
</tr>
<tr>
<td>High density cholesterol</td>
<td>43.1</td>
<td>41.9</td>
</tr>
</tbody>
</table>

The change in HbA1c was modest, The investigators, however, believe it has clinical relevance.

The intervention was associated with weight loss. (Weight gain often accompanies treatment with glucose-lowering medications.)

These improvements were achieved in individuals who continued treatment with oral drugs.

Conclusion: Treatment of DM-2 for 6 months with a L-GID resulted in a moderately lower HbA1c level. L-GID may be useful as part of the strategy to improve glycemic control in patients with DM-2 who are taking antidiabetes drugs.

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*Every little bit helps.*
I doubt, however, that many primary care patients would long abide with the diet. (Note that 20% of subjects in this enthusiastic trial dropped out.) It is easier to take another pill.

Patients can be advised that L-GID does help to improve control and reduce risk factors.

**DIAGNOSIS**

*It Is Time To Move Beyond The Binary Diagnostic Thinking That Has Dominated Medicine For So Long*

**8-1 AGAINST DIAGNOSIS**

The concept of diagnosis is essentially binary. You either have a certain disease, or you do not.

Consider cardiovascular disease, type 2 diabetes, depression, obesity, autism, back pain, arthritis, cancer, and HIV. The authors contend that all except HIV are continuous, reflecting a range of severity. Categorizing patients as having, or not having, the disease depends on choosing a somewhat arbitrary cut point of severity. The definition of hypertension currently includes a systolic pressure of 140 or higher. But there is no particular biological relevance of 140 such that individuals with a BP of 141 differ qualitatively from those with a BP of 139.

The authors propose that thinking about disease in terms of risk prediction is often superior to thinking about disease in terms of diagnosis. The risk prediction alternative uses a statistical model to estimate the probability that a patient will have a clinically important event within a certain period.

Prediction models have 2 particular advantages over our standard way of thinking about diagnosis:

1) They take into account patient preferences
2) They can incorporate multiple patient characteristics

The risk prediction model is not new. Physicians have traditionally called on multiple variables to risk-stratify patients, usually weighing each variable on the basis of clinical judgment and experience. Many diseases include some measure of risk stratification. The use of prediction models adds a quantitative estimate to group patients according to risk, and aids physicians’ process of risk adjustment. Prediction models give physicians explicit information to use in shared decision-making with patients.

Despite the provocative title of this perspective, the authors are not against diagnosis. There are many diseases which are either present or absent. A patient has syphilis or does not. The harms of untreated syphilis cannot seriously be compared with those of penicillin.

Prediction modeling may be more difficult to implement than the diagnostic approach. It is easier to classify patients as having hypertension or not, and to prescribe treatment accordingly, than to enter BP into a calculation of a predicted risk, explain to the patient what this risk means, and then make a shared decision about treatment.

Prediction depends on the availability of a good model. Most models have been evaluated only with regard to their accuracy. Whether use of a model, even a relatively accurate one, would improve an outcome is not entirely clear.
Nonetheless, an approach based on risk prediction can be of great value for many diseases of greatest concern in industrialized countries. Many disorders are best suited for a risk prediction approach. Classification of these complex disorders exists on a continuum perhaps best understood in terms of risk for associated outcomes.

It is time for us to move beyond the binary diagnostic thinking that has dominated medicine for so long and embrace a quantitative approach.

I enjoyed this article.

I believe most primary care clinicians do consider risk prediction. During a consultation, however, primary care clinicians may concentrate on one risk factor and neglect others.

Most patients do not understand the concept. Patients tend to concentrate on one risk factor (eg, cholesterol, BP).

It takes more time to approach patient care from the aspect of risk prevention. In this medical era, prevention and lowering risk of chronic disease predominates. Patients must understand that their health depends on consideration of many risk factors, and respond by treating all of them.

Reducing all risk factors as much as possible, even if the cutpoint is not reached, will likely reduce risk more than treating one factor and reaching its cutpoint.

One of the greatest challenges for primary care is to get patients to take charge of their own health. by reducing lifestyle risk factors. Patients need not improve their lifestyles to a cutpoint. I believe small improvements in diet, BMI, physical activity and adherence to medications when added, will improve prognosis despite not reaching target levels. The exception is smoking. It is either a yes or no risk.

During each consultation, in addition to attention to the primary complaint, primary care clinicians will benefit the patient by briefly listing their life-style risk factors as time and the situation permit.

**DIASTOLIC HEART FAILURE** (See HEART FAILURE [7-2])

**DIVERTICULAR DISEASE**

_Does Not Increase Risk Of Diverticulitis And Diverticular Bleeding_

**8-4 NUT, CORN, AND POPCORN CONSUMPTION AND THE INCIDENCE OF DIVERTICULAR DISEASE**

Historically, physicians have advised individuals with diverticulosis to avoid nuts, seeds, popcorn, corn and other high-residue foods. The recommendation comes from the theory that luminal trauma is a causal mechanism for both diverticulitis and bleeding. Stool may lodge within a diverticulum, obstruct the neck, or abrade the mucosa, and precipitate inflammation or bleeding. Nuts and the other foods are presumed to be particularly likely to abrade the mucosa or to lodge within small diverticula.
This study determined whether consumption of nuts, corn, or popcorn is associated with complications of diverticulosis. It included over 47,000 men aged 40 to 75 who were free of diverticulosis or its complications at baseline. All returned a food-frequency questionnaire which included average frequency of consumption of nuts, corn, and popcorn.

Frequency categories for total consumption of these foods were collapsed into 4 categories: 1) less than once a month, 2) 1 to 3 times a month, 3) once a week, and 4) 2 or more times per week. (27% of participants reported eating nuts at least twice a week.)

During 18 years of follow-up, there were 801 incident cases of diverticulitis, and 383 incident cases of diverticular bleeding.

Nut, corn and popcorn consumption was not associated with an increased risk of complicated diverticular disease. Instead, an inverse relationship was observed. After adjustment of other known and potential risk factors for diverticular complications, the hazard ratios (HRs) of men with the highest consumption compared with the lowest consumption were 80/100 for nuts, and 72/100 for popcorn.

No associations were seen between corn consumption and diverticulitis, or between nut, corn, or popcorn consumption and diverticular bleeding.

Although the study was unable to assess the total seed intake, it did examine the relationship between combined strawberry and blueberry consumption. (The small seeds found in berries have been implicated in diverticular complications.) The HRs of consumption at least twice per week vs less than once a month were 87/100 for diverticulitis, and 86/100 for diverticular bleeding. (Again, a possible protective effect.)

A recent survey reported that about half of colorectal surgeons felt that patients with diverticular disease should avoid these foods. Foods with poorly digested particles are presumed to be particularly abrasive, and apt to lodge within diverticula.

Although fecal matter is commonly found within wide-necked diverticula, the relationship between the ingestion of a particular food and subsequent trauma to a diverticulum is largely speculative.

The exact mechanisms leading to diverticular complications are not known.

Conclusion: These results suggest that consumption of nuts, corn, and popcorn is not associated with an increased risk of diverticulitis or diverticular bleeding.

In the mind of the American public, nuts and seeds are associated with risk of diverticulitis.

How should primary care clinicians respond to this new information, given that nuts are part of the healthy diet?

I would not tell patients who fear diverticulitis or a recurrence of diverticulitis, especially those who have been advised to eliminate them from their diet that they should begin to eat nuts and seeds. Should symptoms recur, even though "scientifically" not associated with ingestion of these foods, blame would fall on the food and clinician alike.
DRUG TREATMENTS

Both Benefits And Risks Need To Be Evaluated And Integrated During The Entire Market Life Of A Drug

11-8 BENEFITS AND RISKS OF DRUG TREATMENTS: How to combine the best evidence on benefits with the best data about adverse effects

The US Institute of Medicine states that a life-cycle approach to drug evaluation is needed. Both benefits and risks need to be evaluated and integrated during the entire market life of a drug.

To understand the full spectrum of adverse effects—those that occur late, that are not known beforehand, and that are rare but nevertheless serious—and to be able to investigate the true incidence of known adverse effects in circumstances of actual prescribing, well designed observational studies will be necessary.

Guidelines from the Agency for Health Research and Quality clearly separate the use of observational evidence for beneficial effects, for which the possibilities are scant; and the use of the same type of evidence for harms, for which the possibilities are rich.

For a future that combines benefit and harm assessment, systematic reviews will need to incorporate the best information from both randomized and observational studies.

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This bears repeating:

Efficacy (as determined by RCTs) answers the question—Can it work?

Effectiveness (as determined by observational studies) answers the question—Does it work in the general population? Is it generalisable?

Efficiency (as determined by cost-effectiveness studies) answers the question—How much does it cost?

“Pragmatic trials” also attempt to judge if results are generalisable to the population.

There have been many accepted drugs and interventions, which have become entrenched in medical practice, that later were found to be misleading. For example:

The long-held view that estrogen prevents cardiovascular events.

The recent discovery that rosiglitazone is harmful to the cardiovascular system.

Primary care clinicians should wait for 2 to 3 years before prescribing a new drug unless the application of the drug is unique and important and if there is no reasonable substitute.
END-OF-LIFE DISCUSSIONS (See BEREAVEMENT [10-3])

EPILEPSY

“According To This Study Of Low-Risk Patients, The Risks Of Seizure Relapse Are In Fact Small.”

8-10 ANTIEPILEPTIC DRUG WITHDRAWAL IN SEIZURE-FREE PATIENTS

The ultimate goal of epilepsy treatment is to become seizure free and have a healthy life without the need to take antiepileptic drugs.

A benchmark study (the Akershus study) was published in Epilepsia in 2008:

Randomized 160 adult patients who were taking a single antiepileptic drug and who were seizure free for more than 2 years to:

1) Withdrawal
2) No withdrawal

Follow-up for 12 months or until seizure relapse:

Seizure recurrence:

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<tr>
<td>1) Withdrawal</td>
<td>15%*</td>
</tr>
<tr>
<td>2) No withdrawal</td>
<td>7% *</td>
</tr>
<tr>
<td>3) After a median of 41 months off medication</td>
<td>27%</td>
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(*Difference not statistically significant)

A normal result to all 15 neuropsychological tests improved from 11% to 28% in those withdrawing from treatment. By contrast, the proportion of normal tests decreased from 11% to 9% in those remaining on treatment.

Withdrawal did not affect quality of life and the EEG.

“We now have class 1 evidence about the benefits and risks of withdrawing antiepileptics in seizure-free adults that we did not have before.”

“It is reassuring, and very valuable that, according to this study of low-risk patients, the risks of seizure relapse are in fact small.”

“Patients and physicians are now better equipped to make the difficult decision to withdraw the drug, after taking into account important other factors, such as the preference of the patient, and the sometimes grave social consequences of seizure relapse.”

Primary care clinicians will encounter this problem.

Although the study was small and had limitations, I believe it provides some guidance.

As noted, many patients did not meet the indications for withdrawal. There is no evidence on outcomes for these patients.
Attempting withdrawal is a personal decision. Primary care clinicians and patients now have some basis for their advice and informed decision.

**EVIDENCE-BASED MEDICINE**

*A Commitment To Lifelong Learning Must Be Integral To Ethical Professional Practice*

9-2  **EVIDENCE-BASED MEDICINE (EBM) AND THE MEDICAL CURRICULUM: The Search Engine Is Now As Essential As The Stethoscope**

Today, health professionals cannot rely on what they were first taught if they want the best for their patients. Clinical performance deteriorates over time. A commitment to lifelong learning must be integral to ethical professional practice.

The skills needed to find potentially relevant studies quickly and reliably, to separate the wheat from the chaff, and to apply sound research findings to patient care, have today become as essential as skills with the stethoscope.

Individual practitioners need to be able to find and use the evidence themselves. A 21st century clinician who cannot critically read a study is as unprepared as one who cannot take a blood pressure or examine the cardiovascular system. The medical curriculum should reflect the importance of changing information for today’s practitioner—the necessary skills must be taught and assessed with the same rigour as the physical examination.

We should teach students the anatomy of research and the basic knowledge and skills for evidence-based practice. These basic skills of using (not doing) research—searching, appraising, and applying research evidence to individual patients—should be taught early and applied as an integral part of learning in all years of the curriculum. But, to be integrated with clinical skills, they must also be regularly applied in the clinical setting.

If today’s practitioners are to retain their professionalism, information and appraisal skills need to be improved urgently.

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“Keeping up” is a continuing and major challenge for primary care physicians (PCPs). The question is—how to do it?

I agree with the editorialists’ comments regarding training medical students and residents to find and appraise the evidence themselves, and to decide if the conclusions presented are firmly evidence-based.

I do not believe this extends to primary care. The editorialists place too great a burden on primary care clinicians. We are already time-constrained. PCPs must rely on independent experts who have the
time and skill to interpret and condense the evidence without bias. The local medical librarian and informal consultations with local specialists can be helpful. Trying to access the evidence through a search engine (eg, through GOOGLE) may lead to overwhelming confusion. There are periodicals and digests available to help us to keep current. Some scan the literature frequently, and assess the evidence rigorously and reliably.

PCPs’ responsibility is to interpret the evidence as it applies to their individual patient. Their job is to develop an empathetic relationship with the patient, determine the patient’s goals and willingness to comply with a medical program, fully inform the patient about benefits, harms and costs of an intervention, and to negotiate his acceptance or rejection. There is no guarantee an individual patient will benefit from application of the best of EBM. Indeed it may cause harm.

Whatever the evidence, value and preference judgments are implicit in every clinical decision. Clinical decisions must not only attend to the best available evidence, but also to the values, and preferences of the informed patient that refer to patients’ perspectives, beliefs, expectations, and goals. “Patient participation in decision-making is a patient’s right.”

There may be 100 reasons why an individual patient does not fit the pattern of a randomized, controlled trial (RTC). PCPs should not place too much faith on the ever-changing and sometimes conflicting evidence of the best of EBM. EBM is a work in progress. It can be a fickle mistress.

There may be good reasons why the best evidence cannot be applied to an individual patient.

1) Costs of the intervention may be too high. The patient may be uninsured.
2) The patient may be medically illiterate. He may not understand.
3) There may be a language barrier.
4) The patient may be non-compliant. The application may be considered too burdensome and inconvenient.
5) Risks may outweigh benefits for an individual. If the number needed to treat to benefit one patient = 24, 23 patients will be exposed to the harms and costs of the intervention without benefit. Patients should understand this.
6) Guidelines, based RCTs may quickly become obsolete. (Some say, on average, they change every 5 years.)
7) The results of a trial may not be generalisable. The individual patient may be included in the many exclusions all RCTs contain.
8) The evidence from different trials may be conflicting.
9) Many trials report surrogate outcomes. They may not determine clinical outcomes.
10) Many trials are biased. Relative to not-for-profit funding, researchers funded by industry
may interpret results differently and in favor of the industry product. (When abstracting an article on drug effects, I always look for the funding source. If it is a drug company, I automatically, perhaps unfairly at times, look for bias. Sometimes “spin” is painfully evident.)

11) RCTs may downplay adverse effects.
12) RCTs may stress statistical outcomes when clinical outcomes are dubious.
13) RCTs may emphasize relative risk reductions and downplay absolute risk reductions.
14) RCTs may be based on a small sample size with limited power.
15) RCTs may emphasize the new and neglect the old.
16) All trials have exclusion criteria. If the individual patient fits one of the exclusions, how does the PCP proceed?
17) RCTs may present a nebulous and complex treatment in the intervention or control group.
   What is cognitive behavioral therapy; a graded exercise program; salt restriction; a stroke unit; low fat diet; telephone counseling? Many authors are willing to supply more detailed information on request. (Drug trials are usually more specific.)

Some of these comments are based on PROGRESS IN EVIDENCE-BASED MEDICINE
JAMA October 15, 2008; 300: 1814-16 first author Victor M Montori, College of Medicine, Mayo Clinic, Rochester, MINN

EXERCISE (See OBESITY [7-2] )

FALLS

“A Successful Translation From Research To Clinical Practice.”

7-4 EFFECT OF DISSEMINATION OF EVIDENCE IN REDUCING INJURIES FROM FALLS

Falling is a common, morbid, and expensive health condition among elderly persons. Effective strategies to prevent falls have been identified, but are underutilized. Falls account for about 10% of ED visits, and 6% of hospitalizations among persons age 65 and older, and are major determinants of functional decline, nursing-home placement, and restricted activity.

This study encouraged clinicians and facilities to incorporate evidence of intervention techniques into practice. The study compared rates of serious fall-related injuries and use of medical services following interventions for prevention vs usual care among persons age 70 and over.

Using a non-randomized design, compared two large regions in Connecticut:
1) Region where clinicians had been exposed to interventions to change clinical practice (intervention region)

2) Region where clinicians had not been exposed to such interventions (usual-care region).

The intervention region included 212 primary care offices (with 522 primary care clinicians including physician assistants and advanced practice nurses). The region also included 133 outpatient rehabilitation facilities, 26 home care agencies, 7 acute care hospitals, and 43 senior centers.

The recommended strategies for preventing falls included a reduction in medications, management of postural hypotension, management of visual and foot problems, hazard reduction, and balance gait, and strength training. Clinicians were encouraged to incorporate assessments, treatments, and referrals into their practices, as appropriate to their discipline and setting.

Enlisted help of media attention (TV, radio, and newspapers), web sites, posters, brochures, educational materials for patients, and advertising on buses to increase awareness; enlistment of opinion leaders to influence colleagues, and visits (outreach) to everyone in the main group of clinicians and facilities to explain evidence-based fall-related practices, and demonstrate how to incorporate fall prevention into their practices.

Rates of serious fall-related injuries per 1000 person years:

A. Pre-intervention—31.2 in the usual care region, and 31.9 in the intervention region.
B. During the intervention period—31.4 in the usual care region, and 29.6 in the intervention region.

This represents an adjusted 9% decline in the rate of serious fall-related injuries.

Differences between regional rates persisted after the reported study period. Three years after the intervention, and one year after the evaluation period, rates of serious fall-related injuries per 1000 person-years were 30.9 in the usual care region and 28.6 in the intervention region.

“Relative rate reductions of 9% in serious fall-related injuries and 11% in fall-related use of medical services represent a successful translation from research to clinical practice.” The 11% reduction represents about 1800 fewer emergency department visits or hospital admissions.

“Our findings . . . suggest that the dissemination of evidence to clinicians about fall prevention when coupled with practice-change interventions results in the adoption of effective strategies to prevent falls and may reduce the number of falls and injuries.”

Conclusion: Dissemination of evidence about fall prevention, coupled with interventions to change clinical practice, may reduce injuries in elderly persons.

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This is a remarkable community-wide effort. I congratulate everyone concerned

I doubt the lone primary care clinicians could fully apply these efforts to their patients. It would be an added burden without adequate compensation

This requires a team effort. Perhaps local Public Health Services or Hospice-Palliative Care could intervene to apply these interventions in a select number of elderly persons and their families
GENERIC DRUGS

“Similar In Nearly All Clinical Outcomes.”

12-2 CLINICAL EQUIVALENCE OF GENERIC AND BRAND-NAME DRUGS USED IN CARDIOVASCULAR DISEASE A Systematic Review and Meta-analysis

Generics are chemically equivalent to their brand-name counterparts in terms of active ingredients. They may differ in specific manufacturing processes. The FDA requires generics to be “biologically equivalent”—defined as absence of a significant difference in the availability of the active ingredients at the site of drug action. Bioequivalence can be established on the basis of the maximum serum concentration of the drug, the time until maximum concentration is reached, or the area under the curve based on serum concentration as a function of time.

There has been concern that “bioequivalent” generic and brand-name drugs may not be equivalent in their effects on various cardiovascular disease clinical parameters including physiological measures (eg, heart rate and BP), laboratory measurements, and outcomes. Of particular concern are drugs with a narrow therapeutic index (effective dose and toxic dose are separated by a small difference in plasma concentration—eg, warfarin; antiarrhythmic drugs). Anecdotes have appeared in the lay press raising doubts about efficacy and safety of certain generics. Are generics inferior to brand-names?

This study evaluated comparisons of generic and brand-name drugs on these outcomes.

Wide therapeutic index (WTI) drugs:

Considered 7 different drug classes (mainly beta-blockers, diuretics, and calcium blockers).

Clinical equivalence was noted in randomized, controlled trials (RCTs) of:

7 of 7 beta-blockers
10 of 11 diuretics
5 of 7 calcium blockers
3 of 3 antiplatelet agents
2 of 2 of statins
1 of 1 ACE inhibitors
1 of 1 alpha blockers.

Narrow therapeutic index (NTI) drugs:

Clinical equivalence was noted in RCTs of:

1 of 1 class I antiarrhythmic agents
Among 43 editorials, 23 (53%) expressed a negative view of generic drug substitution; 12 (28%) encouraged substitution of a generic. Among NTI drugs, 12 expressed a negative view; 4 supported substitution.

Conclusion: Evidence does not support the notion that generic drugs used in cardiovascular disease are inferior to brand-name drugs. A substantial number of editorials, however, counsel against interchangeability of generic drugs with brand-name drugs.

Many pharmacies now offer a long list of generics for $4 for a month’s supply ($10 for 3 months). This appreciably increases the benefit/harm-cost ratio of the drug. It will increase compliance and generalizability because many patients cannot afford costs of brand-name drugs. For example, my pharmacy charges $1.17 for 5 mg coumadin; about 10 cents for generic warfarin.

If plans were to prescribe a generic, would it not be advisable to start with the generic? And try to maintain the same manufacturer throughout the treatment period.

Regretfully, I have doubts about generics produced abroad, especially China. Make sure the FDA has rated the drug as bioequivalent. Is every batch of the drug checked for bio-equivalence? I would purchase the generic from a well-known pharmacy. I would not order by mail, or e-mail, especially from a foreign country.

Our primary care free clinic prescribes only generics. Anecdotally, patients do well.

Note that the authors of the article hedged a bit in their discussion. Please read the full abstract.

HEALING SKILLS FOR MEDICAL PRACTICE


Physician’s relationships with patients can have healing effects. Compassion and trusting relationships with patients are the chief delivery vehicle for the scientific interventions of modern medicine.

Relational skills are fundamental to success. Relationships themselves have potential therapeutic value—described in scientific terms as the “placebo effect”—and, in ethical terms, as the center of the healing relationship.

Relationships with patients are a large part of the intrinsic rewards of medical practice.
Despite this recognition, relational skills are rarely studied systematically, and are often consigned to the unscientific and mystified “art” of medicine.

The authors of this study interviewed 50 practitioners regarded by their professional peers as especially good at establishing and sustaining excellent patient relationships. This included 10 non-MD practitioners of complementary and alternative medicine. 50% were women. They were asked: “How do you go about establishing and maintaining healing relationships with your patients?”

“We believe that our interviews reveal a sound preliminary portrait of core relational skills from the practitioner’s perspective.”

Eight themes emerged:
1. Do the little things
2. Take time and listen
3. Be open
4. Find something to like, to love
5. Remove barriers
6. Let the patient explain
7. Share authority
8. Be committed and trustworthy

Read the full abstract.

Although these themes can begin at the first consultation, it takes time to develop them fully. Fortunately, primary care clinicians are more likely to develop long-lasting relationships than specialists. Nevertheless, there is much opportunity for specialists to apply the themes.

Long ago, when I was in training in an academic center, we young-ones were often somewhat dismissive of the older physicians who we thought had a good “bedside manner”, but who did not keep up with the latest in “scientific” medicine. How wrong we were!

Note that half of those interviewed were women. Women are innately more compassionate than men, and are more open in expressing it. Men can learn.

HEARING IMPAIRMENT (See DIABETES [7-6])
HEART FAILURE

“Treat Now By Treating Comorbidities”

7-2 HEART FAILURE WITH PRESERVED EJECTION FRACTION

Nearly half of all patients with HF have a preserved ejection fraction (HFPEF; formerly termed “diastolic HF”). These patients have a high all-cause mortality after hospitalization for HF. Mortality within 1 year is about 25%; and 65% within 5 years. The implication is that adverse outcomes in these patients are driven by worsening HF. This is not necessarily accurate.

Data from observational studies and clinical trials suggest that these outcomes are driven by important comorbidities that are common in patients with HFPEF. These patients are typically elderly (mean age = 75 years), more often are women, and frequently have multiple comorbidities including hypertension, coronary artery disease, atrial fibrillation, diabetes, chronic kidney disease, cerebrovascular disease, obesity, and anemia.

In one trial, during approximately 3 years of follow-up, mortality in patients with HFPEF was due to cardiovascular causes in 72%, and non-cardiovascular causes in 28%. Of those who died of cardiovascular causes, 38% died of sudden cardiac death, 32% due to progressive HF, 7% due to myocardial infarction, and 9% due to stroke. “These results suggest that HF is not the most frequent cause of mortality in patients with HFPEF.”

“Because patients with HFPEF often have important comorbid conditions, and because these comorbidities strongly influence outcomes, clinicians should aggressively identify and treat conditions such as hypertension, CAD, atrial fibrillation, diabetes, chronic kidney disease, and cerebrovascular disease in these patients rather than waiting for new HFPEF-specific treatments to emerge.” Controlling BP is a class-1 recommendation from practice guidelines of the AHA and ACC for patients with HFPEF. One of the most significant beneficial aspects of improved BP control is the reduction in hospitalizations for HF. This benefit has been extended to the elderly who comprise the majority of patients with HFPEF. In the Hypertension in the Very Elderly Trial, aggressive treatment of hypertension in patients over 80 years of age resulted in a decrease in cardiovascular events and improved survival, with the most profound benefit occurring for the HF endpoint.

For practicing clinicians who provide care for patients with HFPEF, the greatest reductions in overall morbidity and mortality may result from treating comorbidities with therapies available now.

Cardiac output (adequate minute volume) is the determinant of HF, not ejection fraction. Unfortunately we do not now have ability to measure cardiac output easily and at low cost.

Controlling BP in the elderly essentially means controlling systolic pressure.

This is another good example of emphasis on treatment rather than prevention. Interventions should be made early in the course of disease, at a much younger age, rather than waiting until decompensate occurs.

The burden falls heavily on primary care.

HIP FRACTURE (See VITAMIN D [8-3] )
HUMAN PAPILLOMAVIRUS

Women with A Negative HPV Test May Safely Be Screened Every 6 Years.

10-2 LONG TERM PREDICTIVE VALUES OF CYTOLOGY AND HUMAN PAPILLOMAVIRUS TESTING IN CERVICAL CANCER SCREENING

Seven primary screening studies included over 24 000 women. All routinely used both cytology and HPV tests. Included only women with adequate cytology and HPV tests at baseline, and with at least one follow-up cytological test. Cytology tests in Europe are commonly recommended every 3 years.

Regarded abnormal cytology as the equivalent of atypical squamous cells of uncertain significance or worse.

Of the original 24 295 women, 381 developed confirmed cervical cancer during 6 years of follow-up.

Cumulative incidence of cervical cancer at 6 years (per 10 000 subjects):

- HPV + / cytology +: 34
- HPV + / cytology -: 10
- HPV - / cytology +: 2.7 (ten patients)
- HPV - / cytology -: 0.27 (one patient)

The cumulative incidence of cancer in those HPV + rose continuously over 6 years. The cumulative rate of cancer in those positive for cytology & negative for HPV remained below 3%.

In patients negative for both tests, the cumulative incidence rate of future cancer during 6 years of follow-up was uniformly low. Double negativity confers a long lasting protective effect.

Conclusion: The consistently low 6-year cumulative incidence rate of cervical cancer among women with a negative HPV test suggests that screening intervals for HPV could safely be lengthened to 6 years. This could at least partially compensate for the increased referral rate resulting from the higher false positive rates of HPV-based screening strategies, especially in younger women.

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Both CIN and HPV can regress. The latter due to development of immunity, especially in younger women.

I believe both tests should be done simultaneously. Note that if both are positive, the rate of progression to cancer over 6 years was about 3 out of 1000.

The tests are more predictive in older women.
INFLUENZA

“A Strategy with Substantial Benefits”

10-4 EFFECTIVENESS OF MATERNAL INFLUENZA IMMUNIZATION IN MOTHERS AND INFANTS

Inactivated flu vaccine is recommended for pregnant women. It is not licensed for infants younger than age 6 months. It is licensed for age 6 to 23 months. Anti-viral drugs for influenza are not licensed for infants under age 1 year.

This study assessed the clinical effectiveness of the inactivated vaccine administered during pregnancy.

Over a 17-month follow-up:

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<th></th>
<th>Laboratory-confirmed influenza</th>
<th>Respiratory illness with fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants of vaccinated mothers (n = 172)</td>
<td>6 cases</td>
<td></td>
</tr>
<tr>
<td>Infants of mothers not vaccinated (n = 168)</td>
<td>16 cases</td>
<td></td>
</tr>
</tbody>
</table>

(Vaccine effectiveness for infants was 63%)

<table>
<thead>
<tr>
<th></th>
<th>Respiratory illness with fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants of vaccinated mothers (n = 172)</td>
<td>110 cases</td>
</tr>
<tr>
<td>Infants of mothers not vaccinated (n = 168)</td>
<td>153 cases</td>
</tr>
</tbody>
</table>

(Vaccine effectiveness 29%)

Among mothers, respiratory disease with fever was reduced by 36% compared with the non-vaccinated.

Clinical effectiveness in infants lasted up to 6 months of age.

The absolute reduction in the rate of illness showed that every 100 immunizations prevented respiratory illness with fever in 14 infants and 7 mothers. Five mothers would have to be vaccinated to prevent a single case of respiratory illness with fever in a mother or infant.

Conclusion: Inactivated influenza vaccine reduced proven influenza illness by 63% in infants up to 6 months of age and averted approximately a third of all febrile respiratory illnesses in mothers and young infants.

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Another illustration of why almost everyone should be immunized against influenza.
IRRITABLE BOWEL SYNDROME

Psyllium, Hyoscine, and Peppermint Oil are Better than Placebo

12-3 TREATMENT OF IRRITABLE BOWEL SYNDROME IN PRIMARY CARE:

Irritable bowel syndrome (IBS) is common and difficult to treat. A wide range of treatments is used: dietary exclusion; fiber supplements; probiotics; antispasmodic drugs; antidiarrheal agents; laxatives; antidepressants; hypnotherapy; and cognitive behavioral therapy.

A high placebo response has been observed. This highlights our ignorance about the cause of IBS.

A systematic review in this issue of BMJ summarizes the effect of three different agents: fiber, antispasmodic drugs, and peppermint oil.

The number needed to treat to benefit one patient:

- Fiber 12 (12 trials)
- Antispasmodics 5 (22 trials)
- Peppermint oil 2.5 (4 trials)

(All were more effective than placebo.)

Peppermint oil (available without a prescription) seemed to be the most promising agent.

The meta-analysis lacked information on the subtype of IBS (constipation predominant, diarrhea predominant, or alternating), drug dosage, and patterns of administration. It provided no guidance on patient selection for a particular agent. This limits clinical applicability.

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Treatment should be based on an individual trial-and-effect response. As the article states, we do not know the pathophysiology of IBS. Reasonably, the choice of the first agent would depend on the predominant symptom. The best approach might be to allow individual patients to choose a treatment option after being informed about the best of available studies. It would be reasonable to choose the least expensive OTC drug first. And then proceeding to a N = 1 trial.

LIFESTYLE

Associated With Markedly Lower Mortality

9-1 COMBINED IMPACT OF LIFESTYLE FACTORS ON MORTALITY

Diet, physical activity, adiposity, cigarette smoking, and alcohol abstinence (and over use) have been associated with risk of chronic diseases. Identifying priorities for clinical and public health efforts, and understanding the magnitude of effects of these risk factors on overall health is fundamental.
The prospective Nurses’ Health Study followed over 77,000 women aged 34 to 59, beginning in 1980. All were free from cardiovascular disease and cancer at baseline.

Periodically assessed:

A. Diet assessed by a 61-item food frequency questionnaire. Nutrient intakes were calculated.
B. Cigarette smoking
C. Physical activity
D. Alcohol consumption
E. BMI (calculated at baseline)

Classified as low risk:

A. Healthy diet on a scale of 0 to 10 (0 = least healthy; 10 = recommended intake). Considered the highest 40% to be at low risk
B. Never smoking
C. Average of 30 minutes per day of moderate physical activity
D. Alcohol consumption less than 15 g per day. (Up to approximately one drink daily.)
E. BMI 18.5 to 25

Determined mortality over 24 years.

Comparing the high risk with the low risk category of lifestyle factors, the estimated population attributable risk of mortality:

A. Cigarette smoking 28%
B. Overweight 14%
C. Lack of physical activity 17%
D. Low diet quality 13%
E. Not having light to moderate alcohol intake 7%

Never smoking, engaging in regular physical activity, eating a healthy diet, and avoiding overweight were each associated with a markedly lower mortality over 24 years. “We estimated the 55% of all-cause mortality, 44% of cancer mortality, and 72% of cardiovascular mortality could have been avoided by adherence to these four lifestyle guidelines. Light to moderate alcohol consumption (up to one drink a day) was also associated with a lower risk of all-cause mortality.”

If the investigators were to repeat the study, I think they would include vitamin D intake and levels as another risk factor.
All of us have heard this message repeatedly over the years. It deserves repetition. I believe educating patients about healthy lifestyles and following their compliance is one of the most important tasks of primary care clinicians. Patients would likely benefit from a hand-out listing the lifestyle risk factors.

As a prerequisite, clinicians should follow the healthy lifestyle themselves.

MEDITERRANEAN DIET

9-3 ADHERENCE TO MEDITERRANEAN DIET AND HEALTH STATUS: A Meta-analysis

This meta-analysis included 12 prospective studies (over 1,500,000 subjects) which reported the association between adherence to the MD and incidence of diseases.

Defined MD by scores that estimated conformity of the dietary pattern with the traditional MD. Values of 0 or 1 were assigned to each dietary component: vegetables, meat, nuts, seeds, legumes, fruits, milk and dairy products. Total adherence scores varied from a minimum of 0 to a maximum of 9 points.

Overall mortality: Each 2-point increase in adherence score was associated with a significant reduction. (Relative risk = 0.91)

Cardiovascular mortality: Each 2-point increase in the MD score was associated with a significant reduction. (RR = 0.91)

Cancer incidence and mortality: Each 2-point increase in the MD score was associated with a significant reduction. (RR = 0.94)

Parkinson’s disease and Alzheimer’s disease: Each 2-point increase in the MD score was associated with a significant reduction (RR = 0.87)

A 2-point increase in the MD score determined a 9% reduction in overall mortality, a 9% reduction in mortality from cardiovascular disease, a 6% reduction in incidence and mortality from neoplasms, and a 13% reduction in the incidence of Parkinson’s disease and Alzheimer’s disease.

Conclusion: Adherence to a MD can significantly decrease the risk of overall mortality, mortality from cardiovascular disease, incidence of and mortality from cancer, and incidence of Parkinson’s disease and Alzheimer’s disease.

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I have not understood what food factors are related to increased or decreased risk of cancers, and why.
The sunny Mediterranean latitude may also be a factor in the original observation of benefit for persons residing in this area. Vitamin D levels are higher among persons who enjoy the sun and are more exposed to it.

The study included little about fish, olive oil, and modest alcohol consumption. All of us know roughly what the MD is. We should be more compliant with the diet. We should add the MD to our continuing recommendations to patients regarding healthy lifestyles.

MIGRAINE

*Migraine with Aura is A Risk Factor for Myocardial Infarction and Stroke. Younger Women with MwA who Have No Cardiovascular Risk Factors May Be at Increased Risk of Ischemic Stroke*

8-6  MIGRAINE, VASCULAR RISK, AND CARDIOVASCULAR EVENTS IN WOMEN.

Migraine with aura (MwA) is associated with an increased risk of ischemic stroke, migraine angina, myocardial infarction, and other ischemic vascular events.

This prospective cohort study was based on data from over 27,000 women in the Women’s Health Study.

It evaluated whether the association between MwA and cardiovascular disease differs according to vascular risk status as measured by the Framingham risk score.

Categorized women as having migraine and not having migraine, classified as to having aura and not having aura.

Five % of women had MwA.

Women with active MwA had increased incidence of cardiovascular events:

Compared with women without migraine, the age-adjusted hazard ratios in women with active MwA:

<table>
<thead>
<tr>
<th>Major cardiovascular disease</th>
<th>1.93</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>1.80</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.94</td>
</tr>
</tbody>
</table>

There was a strikingly different pattern of association for the outcomes of ischemic stroke and myocardial infarction according to their Framingham risk scores:

A. Ischemic stroke:

When women with active MwA were classified according to their Framingham risk scores, those who developed ischemic stroke were more likely to have a low score (ie, were younger and had lower BP and total cholesterol levels).

The age adjusted hazard ratio of these women, compared with women without migraine:

<table>
<thead>
<tr>
<th>Framingham score</th>
<th>Age-adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>3.88</td>
</tr>
<tr>
<td>≥ 10</td>
<td>1.00</td>
</tr>
</tbody>
</table>

B. Myocardial infarction:
When women with MwA were classified according to their Framingham risk scores, those who developed myocardial infarction were more likely to have a high score (ie, were older and had a higher total cholesterol levels).

The age adjusted hazard ratio of these women, compared with women without migraine:

<table>
<thead>
<tr>
<th>Framingham score</th>
<th>Age-adjusted hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1.29</td>
</tr>
<tr>
<td>$\geq 10$</td>
<td>3.34</td>
</tr>
</tbody>
</table>

Women with migraine without aura were not at increased risk for ischemic stroke or myocardial infarction in any of the Framingham risk score groups.

This diametric pattern of association was driven particularly by the increased risk of ischemic stroke among young women (age 45-49) with active MwA who had a low total cholesterol.

In contrast, the association with MI was high among those with high total cholesterol.

The data add to the growing evidence that MwA is associated with increased risk of vascular events. And imply that cardiovascular risk factors should be more carefully sought and controlled.

Conclusion:
Migraine with aura is associated with increased risk of cardiovascular events.

The association between MwA and cardiovascular disease varies by vascular risk status:

A. Risk of MI rose as the Framingham risk score rose.

B. Risk of ischemic stroke was actually lower in those with a high score, and higher in those with a low score. (Ie, in younger women with few risk factors.)

Overall, the risk of a major cardiovascular event in women with MwA was 3.3%; in those without migraine it was 2.5%. Risk for an individual is low. On a population basis, risk is likely high.

To me, the most important message is the risk of stroke in younger women.

What are the implications for primary care?

1) Consider migraine with aura to be a significant risk factor for vascular complications.

2) These patients should be told that they are at increased risk.

3) They should be treated to reduce incidence of migraine with aura.

4) All risk factors should be reduced as much as possible.
OBESITY

“The Inability To Sustain Weight Loss Appears To Mirror The Inability To Sustain Physical Activity.”

7-7  EFFECT OF EXERCISE ON 24-MONTH WEIGHT LOSS MAINTENANCE IN OVERWEIGHT WOMEN

This study examined the effect of exercise of varying duration and intensity on weight loss in overweight adult women during a 24-month period.

Recruited 201 obese and overweight women in 1999 -2003 from a hospital-based weight loss research center. BMI = 27 to 40 (mean = 32); ages 21-45 (mean = 37).

Randomized to 1 of 4 groups based on prescribed leisure time physical activity (LTPA) energy expenditure (moderate 1000 kcal/wk; high 2000 kcal/wk) and exercise intensity (moderate; vigorous):

1) 1000 kcal/wk – moderate exercise
2) 1000 kcal/wk – vigorous exercise
3) 2000 kcal/wk – moderate exercise
4) 2000 kcal/wk – vigorous exercise

Participants were told to reduce intake to 1200-1500 kcal/day. They were encouraged to attend group meetings and receive telephone calls periodically focused on strategies for maintaining eating and exercise behavior.

Weight loss did not differ among the randomized groups. The mean weight loss overall at 6 months was 8%-10% of initial weight, and at 24 months was 5% of initial weight.

The LTPA increased by a mean of 1235 kcal/wk from baseline to 6 months and declined to a mean of only 720 kcal/wk at 24 months. The prescribed differences in LTPA were not sustained in any randomized group.

About 25% of subjects did achieve a loss of 10% at 6 months and sustained the loss for 24 months. This group reported performing more LTPA (1835 kcal/wk; 275 min/wk; 55 min per day for 5 days a week above baseline level.) compared with those who sustained a loss of less than 10%. They were also more compliant with dietary restrictions.

“Thus, the inability to sustain weight loss appears to mirror the inability to sustain physical activity.”

A level of LTPA that may be necessary to sustain weight loss in relatively sedentary overweight adults for as long as 24 months is approximately twice the public health recommendations. “This confirms the level of physical activity that should be targeted for successful weight loss.”

Conclusion: The addition of 275 min/wk of LTPA, in combination with reduction in energy intake, was important in allowing overweight women to sustain weight loss of 10% over a period of 24 months

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This report is discouraging. Despite a high degree of support, (much higher than would generally be available in primary care), the great majority of participants did not maintain the set goals of diet and LTPA. However, a loss of 5% may reduce risk factors in some patients.

It does reset the levels of energy intake and expenditure necessary to maintain weight loss.
Despite the discouragement, primary care clinicians must continue to encourage weight control, first by maintaining it themselves.

I wonder—how long after the initial 2 years would weight loss be maintained?

The Volume Eaten Is Predicted By The Volume Served.

11-4 THE JOINT IMPACT ON BEING OVERWEIGHT OF SELF-REPORTED BEHAVIORS OF EATING QUICKLY AND EATING UNTIL FULL

Eating quickly, gouging, and binge eating have been associated with increased total energy intake, and may lead to overweight and obesity.

This study examined whether eating until full (eating a large amount of food in one meal) and eating quickly are associated with overweight.

A cross-sectional survey in Japan of over 3200 adults (mean age 53) was carried out in two Japanese communities (2003-2006). All completed a self-administered questionnaire on diet history to assess dietary habits during the previous month. Asked whether they usually eat until full (yes or no) and speed of eating (very slow, slow, medium, fast and very fast).

Multivariate adjusted odds ratios of men for being overweight: (Similar OR for women.)

<table>
<thead>
<tr>
<th>Not eating until full</th>
<th>Eating until full</th>
<th>Eating quickly</th>
<th>Eating until full</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not eating quickly</td>
<td>Not eating quickly</td>
<td>Not eating until full</td>
<td>Eating quickly</td>
</tr>
<tr>
<td>Odds ratio</td>
<td>1.00</td>
<td>1.61</td>
<td>1.42</td>
</tr>
</tbody>
</table>

Those eating quickly and eating until full had 3 times the risk of overweight.

The effect of our food environment on children is likely to be challenging for the future health of the population. As with adults, there is little evidence of short-term energy regulation in the face of changing environmental stimuli. The capacity for regulation seems to decrease as children age. A study of preschool children found that the strongest correlate of the amount of food consumed at a meal was the amount served, and that the amount consumed was not influenced by energy consumed as snacks between meals.

The majority of parents encourage children to eat more than they may have wanted. As a result many children eat substantially more. It seems likely that any early capacity for energy regulation may be overridden by parental pressure to eat more.

Because children find it difficult to regulate their energy intake, it is important to inform parents of the environmental stimuli that promote positive energy balance such as serving excessively large meals.

Conclusion: Eating until full and eating quickly were associated with overweight in Japanese men and women. The combination may have a substantial impact on being overweight.
Sitting down together, enjoying a meal, and discussing the events of the day is, I believe, one of the most important means of facilitating family cohesiveness. Relax and enjoy each other!

Children will copy the habits of their parents.

The old admonition “clean up your plate” is certainly out of date now.

Serve small portions and eat slowly. Be a good role-model for your children. Take care of yourself.

The recent effort to limit snack foods, especially fructose-containing soft drinks, at school is welcome.

Both Associated With Increased Risk Of Death

11-5 GENERAL AND ABDOMINAL OBESITY AND RISK OF DEATH IN EUROPE

Waist circumference and waist/hip ratio, indicators of abdominal obesity, may be better predictors of the risk of disease than the BMI.

Current guidelines with respect to obesity recommend the measurement of waist and hip circumference, and propose cutoff points of 102 cm for men and 88 cm for women. And cutoff points for waist/hip ratio of 100/100 for men and 82/100 for women to define abdominal obesity.

Does the distribution of body fat contribute to the prediction of death?

This study entered and followed over 359,000 men and women age 25 to 70 at enrollment (1992-2000). All were recruited from the general population. At baseline, all participants underwent anthropological measurements and completed a questionnaire about socioeconomic and lifestyle characteristics. Ascertained causes and dates of death over 10 years. Examined the associations of BMI, waist circumference, and waist/hip ratio with risk of death.

The lowest risk of death was at a BMI of 25 for men and 24 for women.

Waist circumference and waist/hip ratio were strongly associated with relative risks (RR) of death: Circumference: RR of death in the highest quintile vs the lowest was 2.05 for men and 1.78 for women. Waist/hip: RR of the highest quintile vs the lowest was 1.51 for men and 1.66 for women.

Among persons with “normal” weight (BMI 18.5 to < 25), the relative risks in the highest quintile of circumference, as compared with the lowest quintile were 2.06 and 1.79.

General obesity was more strongly related to risk of death among participants who had never smoked, whereas underweight was more strongly related to risk of death among current smokers.

Conclusion: General and abdominal adiposity were associate with increased risk of death. This
supports the use of waist circumference and waist/hip ratio in addition to BMI in assessing risk of death.

Measurement of waist circumference is simpler than the ratio. Indeed, measurement is not necessary for many patients. Abdominal obesity is self-evident.

If your weight is “normal”, but your abdominal girth is high, you are at increased risk.
If you are skinny and your abdominal girth is high, you are at increased risk.
Formerly, I considered persons at lower BMIs (eg, 20) to be at lower risk. Several studies now suggest the most favorable BMI is 24-25.

If the patient has a high waist circumference, what can the patient and the primary care clinician do about it? I suspect, very little.
The extra-abdominal fat (exterior to the muscular abdominal wall) is metabolically inert compared with the intraabdominal fat.

ORAL HEALTH (See DIABETES [12-6] )

OSTEOPOROSIS

To Prevent Further Bone Loss And To Reduce The Risk For Initial And Subsequent Fracture

9-7 PHARMACOLOGICAL TREATMENT OF LOW BONE DENSITY OR OSTEOPOROSIS TO PREVENT FRACTURES: A Guideline from the American College of Physicians.

Recommendation 1: ACP recommends that clinicians offer pharmacological treatment to men as well as women who have known osteoporosis, and to those who have experienced fragility fractures. (Strong recommendation; high quality evidence)

Recommendation 2: ACP recommends that clinicians consider pharmacologic treatment for men and women who are at risk for developing osteoporosis. (Weak recommendation; moderate quality evidence.)

Recommendation 3 ACP recommends that clinicians choose among pharmacologic treatment options for osteoporosis in men and women on the basis of an assessment of risks and benefits in individual patients. (Strong recommendation; moderate quality evidence.)

Good evidence supports the treatment of patients with known osteoporosis to prevent further bone loss and to reduce the risk for initial and subsequent fracture.
Bisphosphonates are FDA approved for prevention and treatment. Bisphosphonates reduce risk of vertebral, non-vertebral, and hip fractures. They are reasonable options as first-line therapy especially for patients who have high risk for hip fracture. Estrogen also reduces risk of these fractures, but is associated with serious risks.

There is strong evidence of a modest effect of calcium and vitamin D. Most trials of other drugs included their use. ACP recommends adding them.

Further study is needed on prevention strategies in both men and women and the appropriate duration of treatment for osteoporosis.

Practical Pointers has favored articles on osteoporosis and osteopenia. I believe prevention (contrasted to treatment) is a major opportunity for primary care. The chief risk factor is age. As patients age, bone loss continues, finally affecting everyone. Thus, prevention (as for cardiovascular disease) is a major public health opportunity.

I believe that, if bisphosphonates were started in low dose at an early age and continued, much of the osteoporosis problem would disappear. Why not prescribe a “polypill” for prevention of osteoporosis which would be taken universally beginning at age 60? The pill would contain 800 IU vitamin D3, 1000 mg calcium, and a very low dose of a bisphosphonate.

This would have to be given empirically. It would take years to conduct a trial to prove or disprove effectiveness.

The article notes that bisphosphonate trials have not lasted longer than 5 years.

Certainly, vitamin D and calcium supplements should be started at an early age.

**1200 Mg Of Calcium Daily Had Beneficial Effects On BMD; 600 Mg Did Not**

**11-3 RANDOMIZED, CONTROLLED TRIAL OF CALCIUM SUPPLEMENTATION IN HEALTHY, NON-OSTEOPOROTIC, OLDER MEN**

Calcium supplementation is widely regarded as a fundamental component of the prevention and treatment of postmenopausal osteoporosis in women. It has been assumed that calcium plays a similar role in men who have osteoporosis. The US Surgeon General recommends increases in calcium intake across the entire population, including men.

There has been no consistent evidence, however, that calcium supplements affects bone mineral density (BMD) in men.

This double-blind, randomized, controlled trial followed 323 healthy men (mean age 57) for 2 years. Randomized to: 1) placebo; 2) 600 mg calcium daily; 3) 1200 mg calcium daily [600mg twice
daily]. None received vitamin D supplements.

At baseline (means):

- Calcium intake: 850 mg/d
- Serum 25-OH vitamin D: 37 ng/mL (SI reference = 18-36)
- Bone density T score:
  - Lumbar spine: +0.2
  - Hip: -0.2 (Not osteopenic or osteoporotic.)

Over 2 years, BMD increased at all sites in the group receiving 1200 mg/d by 1% to 1.5% compared with placebo. Lumbar spine BMD increased by 1.2% in the first 6 months, followed by a more gradual increase over the 2 years to 1.5%. BMD in those receiving 600 mg did not differ from placebo.

“The present data establish that 1.2 g of calcium given in a divided dose produces substantial benefit to BMD throughout the skeleton in vitamin-D-sufficient men.”

Conclusion: Calcium, 1200 mg/d had beneficial effects on BMD in men comparable with those found in postmenopausal women; 600 mg /d was ineffective.

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The problem of osteopenia and osteoporosis in older men is becoming more publicized. Vitamin D and calcium supplements are as necessary as in women.

Auckland, the site of the study, is a northern city in NZ, closer to the equator. Its latitude is 37° south, a sunny climate. I doubt that the oral intake of vitamin D is any greater than any other city. Perhaps the sunlight maintained serum levels of 25-OH D.

Note that the mean dietary intake of calcium was 850 mg. When 1200 mg is added, the total grows to over 2000 mg. A two-year period is not long enough to detect adverse effects of this total intake.

The rapidity of increase in BMD surprised me.

PERCUTANEOUS CORONARY INTERVENTION

“PCI Is Not Always Essential For The Relief Of Symptoms In Patients With Stable Angina.”

8-8 EFFECT OF PCI ON QUALITY OF LIFE IN PATIENTS WITH STABLE CORONARY DISEASE.

This study (2008), derived from the COURAGE trial (2007), reports outcomes based on an angina questionnaire score.

Randomized over 2200 patients with stable CAD to:

1) Percutaneous coronary intervention (PCI) + optimal medical therapy, or
2) Optimal medical therapy alone.

Optimal medical therapy (OMT-alone) included:

1) Aspirin (added clopidogrel for those undergoing PCI)
2) Anti-ischemic therapy: long-acting metoprolol, amlodipine, and isosorbide, alone or in combination
3) Statin drug: simvastatin
4) Either lisinopril (an ACE-inhibitor) or losartan (an angiotensin II blocker)

Assessed angina-specific health status with the use of the Seattle Angina Questionnaire (SAQ) and overall physical and mental function with use of the RAND 36-item health survey.

Patients who were free of angina (%):

<table>
<thead>
<tr>
<th>Time</th>
<th>PCI + OMT</th>
<th>OMT-alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>21</td>
<td>23</td>
</tr>
<tr>
<td>One month</td>
<td>42</td>
<td>33</td>
</tr>
<tr>
<td>6 months</td>
<td>56</td>
<td>47</td>
</tr>
<tr>
<td>One year</td>
<td>57</td>
<td>53</td>
</tr>
<tr>
<td>Two years</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>Three years</td>
<td>59</td>
<td>56</td>
</tr>
</tbody>
</table>

Scores on the SAQ were similar between groups at baseline.

In both groups, the percentage of patients who became angina-free increased substantially by one month, and continued to improve thereafter.

During follow-up, the percentage of angina-free patients was significantly higher in the PCI + OMT group than in the OMT-alone group. The difference was not statistically significant at 36 months.

On the RAND-36, a greater proportion of patients who received PCI + OMT had clinically significant improvements in physical function, anginal frequency, and quality of life for the first 6 months. These differences were no longer significant at 12 months.

At 3 months, among patients with the SAQ scores at baseline which indicated the most severe angina, there was a greater benefit from PCI + OMT vs OMT-alone. There was also a clinically significant improvement related to PCI + OMT in those with less severe angina. Among those with the least angina or no angina, there was no difference in improvement between groups.

Unexpectedly, during the first 6 months, there was a significant and rapid improvement in the SAQ among patients in the OMT-alone group,

“This finding with respect to the benefit of optimal medical therapy alone shows that PCI is not always essential for the relief of symptoms in patients with stable angina.”

Throughout the follow-up period, the mean differences between treatment groups on the SAQ scales were small. However, likelihood of clinically significant improvement from baseline was greater in the PCI + OMT group during the first six months (though not thereafter).
Conclusion: Patients with chronic coronary disease may expect relief from angina whether they are treated with PCI + OMT or with OMT-alone. An initial strategy of PCI + OMT relieved angina and improved self-assessed health status to a greater extent than an initial strategy of OMT-alone for approximately 24 months, but not thereafter.

A greater benefit from PCI + OMT was observed in patients with more severe and frequent angina.

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OMT is required for all patients with angina.

Primary care clinicians will see patients with angina. This study will help them to classify and advise the patient accordingly. Clinical judgment by the primary care clinician, and a fully informed patient are essential. If the angina is severe, immediate consultation for PCI is advisable. Those with less severe angina can be given a choice. (I believe many patients will resist intervention.) Borderline patients may be started on a strict OMT program and rechecked for improvement within 1 and 3 months.

Note that almost ½ of patients in both groups still experienced angina at 3 years. The study did not concern these patients.

POLYPILL

10-11 WHAT HAPPENED TO THE POLYPILL?

In 2003, Wald and Law published an article describing a “polypill” which they stated would reduce incidence of heart attacks and stroke by 80%. The pill was to be taken by everyone over the age of 55 without pre-testing or follow-up. It contained aspirin, a statin, a diuretic, a beta-blocker, an ACE inhibitor, and folic acid—all generics and at low dose. The logic was that most people in Western society are at increased risk of cardiovascular disease, and that the drugs are effective and safe.

Now, more than 5 years later, you might imagine that research groups would be competing to test this innovative suggestion. Not so.

The polypill concept is accused of medicalizing the population. Wald argues that if you test people to see if they have high BP or high cholesterol, they are given a disease label and then must come back regularly to recheck. “You have created a patient.” This is real medicalization—not universal access to a pill.

Does Wall sense a moral objection to use of the pill? He responds: “Is getting a vaccination a moral weakness?”

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I have been fascinated by the polypill concept. It is based on the belief that all persons are at risk of cardiovascular disease. It continues to attract commentary. It seems to me that that a form of the polypill is already being taken by millions of Americans—low-dose aspirin, statins, antihypertensives,
beta-blockers, and ACE inhibitors. But not over the counter, and not in one pill. Modern primary care requires a risk factor to be demonstrated objectively. Drugs are prescribed after tests establish risk, and require periodic follow-up. This magnifies costs and inconvenience.

Some will say that the pill medicalizes the whole population. Is not the whole population being largely medicalized now?

I believe that it takes only a glance to assess millions of persons in this country as being at risk.

I also believe there is little chance that the polypill concept will be tested or approved in the US. There is no commercial interest.

Could not, and should not, primary care clinicians legitimately prescribe a polypill to select patients?

PREVENTIVE THERAPY

Clinicians Face Challenges In Applying Preventive Interventions.

12-1 IS CLINICAL PREVENTION BETTER THAN CURE?

In wealthy countries, the focus of clinical care is changing from cure to prevention—to anticipate future disease in currently healthy persons. Prevention has an aura of omnipotence and good sense. Is it always true that prevention is better than cure?

This essay reviews the challenges clinicians face in applying preventive interventions.

New thinking is needed about the benefits and potential harms of prevention in clinical medicine. Prevention can cause harm. Potential harms include increased fear and perception of illness when none exists; assuming that prevention is of equal value for everyone; and frustration on the part of clinicians over a growing list of requirements that are impossible to accommodate within the clinical visit.

Many preventive interventions are promoted without sufficient evidence of benefits, cost effectiveness, and feasibility in routine clinical visits.

Prevention can be complex and expensive. Clinicians may find it difficult to carry out the recommended strategies. Labeling almost always heightens anxiety and may lead to other tests and consultations. Drugs, which patients must take for the rest of their lives (a particular concern for young patients with mild hypertension) do not guarantee individual benefit.

Not all preventive activities have the same benefit, adverse effect profile, and costs. Judgment is required in adhering to recommendations, taking into account different biological, cultural, social, and economic contexts, patient’s preferences, the natural history of the disease, co-occurring risks, relative, attributable, and absolute risk, and prevalence in the population.

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Primary care clinicians should consider:

The harms of labeling and the adverse effects of preventive interventions may be high.

Life-style recommendations first. They are associated with low risk. (Also low compliance.)

Intervention should be based on negotiation with an informed patient. (This may be difficult and take time.)

It is difficult for patients to initiate preventive measures and to continue them (eg, seat belts, condoms). Compliance after initial enthusiasm will lag.

Development of the “medical home” potentially will improve application of preventive interventions. One member of the team may assume the responsibility to follow-up, contacting patients periodically to ask if they are complying.

PRIMARY CARE MEDICINE

“More Money Will Not Be Enough To Revitalize Primary Care”

11-1 THE FUTURE OF PRIMARY CARE

The editors of NEJM asked several experts to share their perspectives on the crisis in U.S. primary care. They discuss our problems, suggestions for improvement, and add a comparison with the UK system of primary care.

They recommend extended primary care with expanded teams of professionals (nurses, administrators, as well as M.D.s). Primary care physicians need to learn to work in teams and adjust to the notion that much of primary care can be delivered by non-physician team members.

Patient care delivered with a primary care orientation is associated with more effective, equitable, and efficient health services. Primary care physicians (PCPs) perform many tasks that do not require a medical degree, and could be delegated. Primary care must recapture its attraction for the next generation’s best trainees.

Primary care is not defined by who provides it. Rather, it is a set of functions—first-contact care; person (not disease)-focused care over time; comprehensiveness in attending to the needs of populations, subpopulations, and patients; and coordination of care when services have to be received elsewhere or from others.

Payment reform is necessary. But, “More money will not be enough to revitalize primary care”

Electronic record-keeping is essential.

If the team approach is clearly explained to patients, if patients are offered continuity with the team, and if team members provide patient-centered, high-quality care, it is likely that patients will transfer their trust to the team.
In the UK, primary care physicians hold each patient’s lifelong record, which includes a letter regarding every visit to a specialist.

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Our healthcare system is broken. Can we fix it? How long will it take? I believe the change will not take place until a substantial majority of Americans support it.

Changing emphasis to primary care is more than a sea change. It is a revolution. Supplying a primary-care medical home for all citizens may be an insurmountable task.

Some will cry, “rationing”.

Please read the full abstract.

PROSTATE CANCER

*Individualize Decision-Making To The Specific Patient Or Situation.*

**8-5 SCREENING FOR PROSTATE CANCER: U.S. Preventive Services Task Force Recommendation Statement**

The USPTF makes recommendations about preventive care services for patients *without* recognized signs and symptoms of the target condition.

The USPTF recognizes that decisions involve more consideration than this body of evidence alone. Clinicians should understand the evidence, but individualize decision-making to the specific patient or situation.

Clinical summary of the USPTF recommendations for prostate cancer (PC) screening:

A. Men age 75 and older:

   Do not screen. The USPTF recommends against screening. There is moderate or high certainty that screening has no net benefit, or that harms outweigh the benefits. For men age 75 and older, and for those whose life expectancy is 10 years or fewer, the incremental benefit from treatment of PC detected by screening is small to none.

B. Men younger than age 75:

   No recommendation.

   Current evidence is insufficient to assess the balance of benefits over harms. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

The prostate specific antigen (PSA) is more sensitive than digital rectal examination (DRE). The conventional cut-point (4.0 ug/L) misses some early PC. Lowering the cut-point would increase the rate of false positives. Variations of PSA screening have not yet been demonstrated to improve health outcomes.

Suggestions for practice: Clinicians should discuss the potential benefits and know harms of PSA screening with their patients younger than age 75. They should be informed of the gaps in the evidence, and their personal preference should guide the decision of whether to order the test.
This is a good example of how fashions in medicine change. In the early days of PSA screening, almost everyone climbed on the bandwagon, and screening became routine—often without any discussion with the patient. As a result, many men became obsessed with their “PSA”.

Does this end the discussion? I believe not. Large screening studies are still progressing.

In primary care practice, younger men should be fully informed before a PSA test is ordered.

Do the recommendations apply to digital rectal examinations? I believe not. DRE is not really a screening test for PC. It is included in a routine examination to evaluate benign prostate enlargement as well as rectal carcinoma. If a nodule suggestive of PC is found, further tests and treatment should follow.

“Think Twice, Or Even 3 Times.”

12-7 SCREENING FOR PROSTATE CANCER AMONG MEN 75 YEARS OF AGE AND OLDER

Prostate cancer (PC) screening with prostate specific antigen (PSA) remains one of the most controversial issues in medicine.

The US Preventive Services Task Force (USPSTF) recently revised its recommendation regarding screening, concluding that “the current evidence is insufficient to assess the balance of benefits and harms of prostate cancer screening in men younger than age 75 years”.

Furthermore, it now “recommends against screening for prostate cancer in men age 75 years and older”.

The new recommendations imply that clinicians should discuss the potential benefits and known harms of screening with men between age 50 and 74, but not necessarily with older men.

Why change the recommendations for men over age 75? The task force believes that at least a moderate amount of evidence now makes it possible to conclude that the known harms of screening outweigh the possible benefits in this age group. The risks of postoperative death and complications from radical prostatectomy are age related, escalating above age 75

The new advice is “do not bring up the subject of PSA screening for elderly patients”. Indeed, ordering a PSA at any age without discussing the harms and benefits, and letting the informed-patient decide, is a mistake. Even after age 75, personal choice is important. I would not deny a PSA screen for an elderly man who insists upon it. But, only after a calm discussion of harms and benefits.

This is another good example of how fashions in medicine change. When first introduced, PSA was touted as a major advance.
RENNAL OUTCOMES WITH TELMISARTAN AND RAMIPRIL

“There Was No Evidence Of A Renal Benefit With Combination Therapy.”

8-7 RENAL OUTCOMES WITH TELMISARTAN, RAMIPRIL, OR BOTH, IN PEOPLE AT HIGH VASCULAR RISK

Angiotensin converting enzyme inhibitors (ACE-i; eg, ramipril; Altace; King), and angiotensin II receptor blockers (ARB; eg, telmisartan; Micardis; Boehinger Ingelheim) have been reported to reduce albuminuria as well as renal risk (ie, decrease of glomerular filtration rate, and need for dialysis) in patients with advanced renal disease. Combination therapy has been associated with greater adverse effects than monotherapy (eg, acute renal failure and hyperkalemia).

Inhibition of the renin-angiotensin-aldosterone system by ACE-i or ARB has been reported to preserve renal function better than other antihypertension drugs.

This trial asks—Are the effects of the two drugs equivalent? Does the combination further reduce renal risk?

This large multicenter, randomized, double-blind controlled trial (2001-2007) entered over 25 000 patients. All were over age 55; all had established atherosclerotic vascular disease, or diabetes with end-organ damage.

Randomized to:
1) Ramipril 10 mg daily
2) Telmisartan 80 mg daily. or
3) Both drugs combined.

Primary renal outcome was a composite of dialysis, renal transplantation, doubling of serum creatinine, and death. Secondary renal outcome was dialysis or doubling of serum creatinine.

Also determined changes in surrogate markers such as estimated glomerular filtration rate and proteinuria.

Median follow-up = 56 months.

The number of events for the composite primary outcome was similar for telmisartan (13.4%) and ramipril (13.5%), but was increased with the combination (14.5%). The secondary renal outcome was similar for telmisartan (2.21%) and ramipril (2.03%), and most frequent with combination therapy (2.49%).

Estimated glomerular filtration declined in all 3 groups, least in the ramipril group, most in the combination group.

Serum creatinine showed greater increase with combination therapy than with ramipril. Urinary albumin secretion increased in all 3 groups, most in the ramipril group, least in the combination group.

“There was no evidence of a renal benefit with combination therapy.”

“The observation that combination therapy was associated with more renal outcomes and a faster decrease in GFR than with ramipril alone is of concern.”

Conclusion: In patients at high risk, effects of telmisartan and ramipril on major real outcomes were similar. Combination therapy (compared with either drug alone) worsened renal outcomes.

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Since neither ACE-i nor ARB completely block the renin-angiotensin, aldosterone system, the hope was that combined therapy would be more effective. The investigators must have been disappointed.

Unfortunately, there was no placebo group in this trial. The benefits and harms of therapy with these drugs, as compared to placebo, were not determined.

ROSUVASTATIN  (See STATIN DRUGS [11-2])

SMOKING

If You Are A Heavy Smoker And Live To Age 70, You Will Feel 10 Years Older

10-1 THE EFFECT OF SMOKING IN MIDLIFE ON HEALTH-RELATED QUALITY OF LIFE IN OLD AGE: A 26-Year Prospective Study

Smoking shortens life expectancy by 7 to 10 years. Do smokers who survive experience more years of disability? Are the extra-years gained by not smoking related to a better health-related quality of life (HRQoL)?

This prospective cohort study followed over 1100 men for 26-years. All were healthy at baseline in 1976 (mean age 48). About 1/3 were non-smokers; 2/3 smokers.

Determined total mortality through 2000 and HRQoL of survivors (mean age 73) in 2000.

During follow-up, 22% died. Never-smokers lived a mean of 10 years longer than heavy smokers.

In 2000, only 78 subjects (7%) were still smoking.

There was a graded deterioration of HRQoL with increasing number of cigarettes smoked.

Never-smokers had the highest (best) scores on all 8 of the RAND-36 scales There were especially large differences in the scales of physical functioning, and in role limitations compared with those who smoked over 20 /d (differences = +17% and +16%).

The 78 subjects who survived and continued to smoke in 2000, had poorer scores in all 8 scales compared with the other categories of smokers.

Although many smokers had quit between baseline and 2000, the effect of baseline smoking on mortality and HRQoL in old age remained strong.

Cigarette smoking had a dose-dependent effect on mortality and the RAND scale. Heavy smokers had the worse results for both end points.

“Compared with heavy smokers, never-smokers had a mean life expectancy that was 10 years longer. They also enjoyed significantly better physical health status, which was equal to an age difference of 10 years”
Conclusion: During a 26-year follow-up, HRQoL deteriorated with an increase in daily cigarettes smoked in a dose-dependent manner. Never smokers lived longer and their extra years were of better quality.

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I was impressed with the number of subjects who quit smoking. Does Finland have a superior quit program?

At baseline (mean age 48) smokers had worse perceived health and physical fitness than non-smokers. I presume many began to smoke in adolescence.

Smokers do not experience any increase in the pleasure of living.

Does smoking ever bring benefits? Some who survived extreme stress (eg, war) have stated that they could not have survived without the comfort of cigarettes.

SPIRITUALITY AND PATIENT CARE

Spirituality Is Part Of What It Means To Be Human. Spirituality Is An Important Part Of Medical Care

8-2 MEDICINE, SPIRITUALITY, AND PATIENT CARE.

(Read the full abstract, or better, the original JAMA article. I quote a few passages. RTJ)

Is spiritual care always an important part of medical care? If yes, who should assess the need for it?

Because spirituality is not usually based on human-made laws of reason or logic, it is often described as the non-logical or non-rational part of being human that connects to the sacred—God, the Ultimate, or Universal Principle. The spiritual transcends ordinary human experience. Spirituality is part of what it means to be human.

The healing art of medicine includes, and goes beyond, the science and takes into account what gives a person meaning—his or her loves, priorities, beliefs, fears, dreams, and questions.

The practice of medicine, at its finest, involves far more than knowing the right science; it involves working with the whole person and not just a diseased body part.

For many patients, faith in the supernatural (ie, spirituality) is important—in health and especially in illness. Faith gives meaning to their lives. It provides comfort when their lives are not going well, and it remains when other resources are spent. Faith can support when support is most needed.

At times of vulnerability because of illness many patients want their physician to know what gives them meaning, comfort, and support. Spirituality is an important part of medical care, especially when patients are very ill or dying.

Each physician has his or her own spirituality that gives meaning to life. Although physicians might not believe in a personal God, they might believe in something. It is good for physicians to be cognizant of their own spirituality,

Although physicians do not need to deliver spiritual care, asking questions to discern the spiritual needs of their patients might be in the best interest of both.
Addressing spiritual matters with patients offers a meaningful opportunity to primary care clinicians. Many physicians, especially younger ones, have difficulty in discussing spiritual matters with their patients. Maturity makes it easier.

A simple leading question or statement (Are you at peace?) may broach the subject and make it possible for patients to express their inner thoughts, and bring comfort.

STATIN DRUGS

Is This Applicable To Primary Care?

11-2  ROSUVASTATIN TO PREVENT VASCULAR EVENTS IN MEN AND WOMEN WITH ELEVATED C-REACTIVE PROTEIN

Increased levels of the inflammatory biomarker C-reactive protein (CRP) predict cardiovascular events. Since statin drugs lower levels of CRP as well as cholesterol, these investigators hypothesized that people with elevated high sensitivity CRP, but without hyperlipidemia, might benefit from treatment with rosuvastatin.

This very large multicenter trial (over 1300 sites in 26 countries) screened over 89 000 subjects (men over age 50 and women over age 60). Over 72 000 were excluded for various reasons, leaving 17 802 “apparently healthy” subjects for randomization. (Ie, 4 out of 5 screened were excluded.)

All subjects who were entered had LDL-cholesterol levels below 130 and high sensitivity CRP levels 2.0 mg/L or higher. The authors state: “Nearly all study subjects had lipid levels at baseline that were well below the threshold for treatment according to current prevention guidelines.” (See full abstract for details. RTJ)

Randomized to: 1) rosuvastatin 20 mg daily (Crestor; Astra Zeneca), or 2) placebo.

Primary endpoint = a first major cardiovascular event (non-fatal myocardial infarction, non-fatal stroke, hospitalization for unstable angina, an arterial revascularization procedure, or death from cardiovascular causes. Follow-up for median of 2 years.

Rosuvastatin was associated with a reduction of LDL-c by 50% and CRP by 37%.

<table>
<thead>
<tr>
<th>End point</th>
<th>Rosuvastatin (n = 8901)</th>
<th>Placebo (n = 8901)</th>
<th>AD</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>Rate per 100-person-yr</td>
<td>No. of patients</td>
<td>Rate per 100-person-yr</td>
</tr>
<tr>
<td>Primary end-point</td>
<td>142</td>
<td>0.77</td>
<td>251</td>
<td>1.36</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>31</td>
<td>0.17</td>
<td>68</td>
<td>0.37</td>
</tr>
</tbody>
</table>

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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>33</td>
<td>0.18</td>
<td>64</td>
<td>0.34</td>
<td>0.16</td>
<td>625</td>
</tr>
<tr>
<td>Death</td>
<td>198</td>
<td>1.00</td>
<td>247</td>
<td>1.25</td>
<td>0.25</td>
<td>400</td>
</tr>
</tbody>
</table>

[AD = absolute difference  NNT = number needed to treat for one year to benefit one patient

My calculations. RTJ. ]

Conclusion: “In this randomized trial of apparently healthy men and women who did not have hyperlipidemia but did have elevated levels of high-sensitivity C-reactive protein, the rates of a first major cardiovascular event and death from any cause were significantly reduced among the participants who received rosuvastatin as compared with those who received placebo.”

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Please read the full abstract.

High sensitivity CRP may be a valid, cost-effective and important risk factor. This trial does not convince me that it is. Rosuvastatin 20 mg vs placebo given to subjects with LDL-c < 130 (disregarding CRP), and lowering LDL-c by 50%, would certainly be associated with an incremental reduction of cardiovascular events. Would risk be lower in those with a high CRP vs those with a low CRP? Would the difference be clinically significant? Would treatment based on CRP alone (high vs low) be associated with clinically important benefit?

Are the results of this trial applicable to primary care practice? I think not:

- Complexity
  1) Including high sensitivity CRP levels in addition to LDL-c adds complexity.
  2) If primary care clinicians followed the procedures of the trial, additional screening would be needed to select patients: hepatic functions, creatine kinase, creatinine. And patients would be excluded on a clinical basis: history of cardiovascular disease, diabetes, uncontrolled hypertension, inflammatory diseases.
  3) Over 1000 subjects would have to be screened to begin therapy in 200.
  4) Primary care clinicians and their patients now have multiple risk factors to treat—without great success. We need to apply those we already have rather than look for others.

- Cost:
  1) A single tablet of rosuvastatin 20 mg now costs $3.45. One a day costs $1259 a year
  2) The money needed to treat (MNT), by my calculation, to prevent one primary endpoint in one year, is 169 X $1259 = $212 771. And a like amount every following year.
  3) The complexity of the treatment would add costs, including the cost of CRP screening.
  4) Generalizability of rosuvastatin therapy would be limited due to cost alone. Most patients could not afford it.
• Adverse effects:

1) Rosuvastatin 20 mg is a moderately high dose. As the investigators state, we cannot now know all adverse effects that will occur over a period of years. There is a hint of an increased incidence of diabetes. Certainly, over time, adverse effects would be more frequent in those receiving 20 mg than in those receiving 5 or 10 mg.

2) To prevent one patient from experiencing a primary endpoint in one year, 168 patients would be exposed, without benefit, to adverse effects of rosuvastatin.

• Considering complexity, costs and adverse effects

I doubt few, if any, fully informed patients would accept this therapy.

The benefit/harm-cost ratio of rosuvastatin is very low.

STROKE

Extends The Time-To-Treatment Window

9-4 THROMBOLYSIS WITH ALTEPLASE 3 TO 4.5 HOURS AFTER ACUTE ISCHEMIC STROKE

Thrombolytic treatment with alteplase initiated within 3 hours after onset of symptoms is the only medical therapy currently available for acute ischemic stroke. Patients so treated were reported to be at least 30% more likely to have minimal or no disability at 3 months than those who received placebo.

This phase 3 trial was designed to test the hypothesis that alteplase can be safe and effective when given 3 to 4.5 hours after onset of symptoms of ischemic stroke.

The trial entered 821 patients (mean age = 60) with acute ischemic stroke. All had onset of stroke symptoms 3 to 4.5 hours before initiation of treatment. All received a CT brain scan before and within 36 hours after treatment. At baseline, none had brain hemorrhage or a major infarction.

Randomized to:

1) Intravenous alteplase (Activase; Genentec) 0.9 mg per kg body weight, given 10% as a bolus intravenously, and the remainder over 1 hour, or

2) Placebo

Primary endpoint = disability at 90 days, dichotomized as a favorable outcome (score 0 to 1 on the modified Rankin scale), or an unfavorable outcome (score 3, 4, 5, or 6).

Secondary outcome = global outcome analysis of 4 neurologic and disability scores combined.

Percentage of patients grouped according to time intervals of receiving treatment after onset:

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 – 3.5 h</td>
<td>10%</td>
</tr>
<tr>
<td>3.5 - 4.0 h</td>
<td>47%</td>
</tr>
</tbody>
</table>
4.0 – 4.5 h  39%

(Median time for administration of alteplase was 4 hours. Time not available in 12 patients

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Alteplase</th>
<th>Placebo</th>
<th>Absolute difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. Primary end point.</td>
<td>52%</td>
<td>45%</td>
<td>7%</td>
<td>14</td>
</tr>
</tbody>
</table>

(Patients with Rankin scores 0 and 1)

B. Secondary outcome—global odds ratio (favoring alteplase)

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Intention to treat</td>
<td>1.28</td>
</tr>
<tr>
<td>Per protocol</td>
<td>1.39</td>
</tr>
</tbody>
</table>

Safety:

Deaths (8%) were equal in both groups and occurred at about the same time intervals.

Incidence of symptomatic intracranial hemorrhage: alteplase 2.4%; placebo 0.3%. All occurred within the first 36 hours

The initial severity of a stroke is a strong predictor of the functional and neurological outcome and the risk of death. Patients with severe stroke were excluded from this trial. It is likely that the milder initial severity of stroke overall among patients enrolled in the trial explains the improved outcomes as compared with other trials.

Conclusion: Intravenous alteplase given within 3 to 4.5 hours after onset of stroke symptoms was associated with a modest, but significant, improvement in clinical outcomes.

There was a higher rate of symptomatic intracranial hemorrhage.

Questions for primary care:

1) How accurately is the time of onset determined? Do patients really know the exact time in most cases? The study excluded patients for whom the time of onset was not known.

2) Is there any attempt to negotiate a treatment plan with the patient or family? Would time limits negate any attempt to explain risks and benefits, allowing the patient to choose?

3) Could primary care clinicians accurately determine severity of the stroke? Would the patient recover just as well without thrombolysis?

4) Would primary care clinicians consider all exclusion criteria? There are 15 listed on page 1320.

I believe this intervention would be extremely difficult for primary care clinicians to apply in their communities. Stroke specialists should be available at local hospitals round the clock, just as cardiologists are available for treatment of acute myocardial infarction.
**11-6  NONFASTING TRIGLYCERIDES AND RISK OF ISCHEMIC STROKE**

Two recent cohort studies reported a strong association between elevated levels of non-fasting triglycerides and increased risk of myocardial infarction, ischemic heart disease, and death.

This study asks, “Are non-fasting triglycerides (NFTG) associated with an increased risk of stroke?

The population-based prospective cohort (Copenhagen City Heart Study), initiated in 1976, included over 13,000 men and women (interquartile age ranges 48 to 57), with follow-up through July 2007 (31 years).

NFTG levels were determined at baseline. All blood samples were drawn between 8 AM and 4 PM; 82% of subjects had eaten within the last 3 hours. The remaining had eaten more than 3 hours before.

During follow-up, 1529 ischemic strokes occurred.

The cumulative incidence of ischemic stroke increased with increasing levels of NFTG.

Multivariate adjusted hazard ratios (HR) for stroke for men according to NFTG levels:

<table>
<thead>
<tr>
<th>NFTG Level</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 89</td>
<td>1.00</td>
</tr>
<tr>
<td>89-176</td>
<td>1.30</td>
</tr>
<tr>
<td>177-265</td>
<td>1.60</td>
</tr>
<tr>
<td>266-353</td>
<td>1.50</td>
</tr>
<tr>
<td>354-442</td>
<td>2.20</td>
</tr>
<tr>
<td>&gt; 442</td>
<td>2.50</td>
</tr>
</tbody>
</table>

There were corresponding values for women. The HR for each 89 mg/dL increase in NFTG was 1.24.

“By using nonfasting rather than fasting triglycerides, . . . we detected associations between linear increases in nonfasting triglycerides and stepwise increases in risk of ischemic stroke with no threshold effect.”

Conclusion: NFTG levels were associated with increased risk of ischemic stroke.

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*It has long been considered that TGs are a risk factor for cardiovascular disease. The association was related to fasting TG. What took so long for us to realize the association with NFTG? One reason NFTG were not used to determine risk was that there was no standard. It is difficult for us to move from an “established” risk factor (fasting TG) to a new one.*

*The relation between NFTG and cardiovascular disease makes sense to me. Will this lead to a renaissance of use of fibrates and niacin? Certainly it emphasizes the downside of high fat meals.*

**TRIGLYCERIDES (See STROKE [11-6] )**
VITAMIN D

Low Concentrations Were Associated With Higher Risk Of Hip Fracture.

8-3 SERUM 25-HYDROXY VITAMIN D CONCENTRATIONS AND RISK FOR HIP FRACTURE

This study tested whether low serum levels of 25-hydroxy vitamin D \(25(\text{OH})\text{D}\) are associated with higher risk of hip fracture.

The study population came from the large Women’s Health Initiative Study (1994-98), which was limited to women age 50 to 79 at baseline. All were postmenopausal. All were community dwelling.

Measured total 25(OH)D in all subjects. (D2 + D3)

Followed all for a median of 7 years for incident hip fracture. Of the over 39,000 eligible women, 404 developed a hip fracture during follow-up.

Cases = 400 women randomly selected from the 404 who sustained a hip fracture during follow-up.

Controls = 400 women without hip fracture randomly selected and carefully matched. (Mean age = 71. None had taken estrogen or other bone-active therapies at baseline.)

Compared 25(OH)D levels in cases and controls.

Mean serum 25-OH-D levels were lower in cases than in controls (56 nmol/L vs 60 nmol/L)
Divided 25(OH)D levels into quartiles and determined odds ratio of hip fracture of the lowest quartile vs the highest:

\[
\begin{array}{ccc}
\text{25(OH)D} & \text{Lowest Q} & \text{Highest Q} \\
9-48 \text{ nmol/L} & 71-122 \text{ nmol/L} \\
\text{Odds ratio of hip fracture} & 1.72 & 1.00 \text{ (reference)} \\
\end{array}
\]

The increased risk for hip fracture was primarily confined to women with the lowest 25(OH)D concentration.
Conclusion: Low 25(OH)D levels were associated with an increased risk for hip fracture in elderly community dwelling women. Lower serum levels might help identify women at high risk for hip fracture.

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This is particularly applicable to primary care because so many patients are deficient.

Recent reports of adverse effects of vitamin D deficiency have been astounding. Practical Pointers has abstracted a number of articles related to vitamin D deficiency over the past few years.

Some authors have linked deficiency to a variety of conditions: breast cancer, colon cancer, rheumatoid arthritis, cardiovascular disease, diabetes, hypertension, multiple sclerosis, muscle weakness, falls, mortality, and premenstrual syndrome, as well as osteoarthritis, osteoporosis, osteopenia. Almost all are speculative and require follow-up and confirmation.

See Practical Pointers:

2008 January [1-7]
2007 July [7-1]; February [2-4]
2006 February [2-4]
2005 March [3-8]; May [5-3]; June [6-14]; November [11-3];
Vitamin D supplementation must have one of the highest benefit/harm-cost ratios of any medication. The cost is very low and the harm nil.

Primary care clinicians are increasingly obtaining vitamin D serum levels in their patients. I believe an alternative for many patients would be to assume the level is low and empirically prescribe supplementation. Dose should be at least 800 IU daily with added calcium.

1 See also “25-Hydroxyvitamin D Levels and the Risk of Mortality in the General Population” Archives Int Med August 11/25 2008; 168: 1629-37 First author Michael L Melamed, Albert Einstein College of Medicine, Bronx, NY

This study was based on the National Health and Nutrition Examination (1988-94), a nationally representative group of adults 20 years of age and older. Serum vitamin D levels were determined at baseline.

During followed for mortality for a median of 9 years, there were 1806 deaths.

Compared with the highest quartile of vitamin D, the lowest quartile (< 18 ng/mL) experienced a 26% increase in death compared with the highest quartile.