

**PRACTICAL POINTERS
FOR
PRIMARY CARE MEDICINE
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JANUARY- JUNE 2010

PRACTICAL CLINICAL POINTS

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO FULL ABSTRACTS

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This index is a reference document based on articles abstracted from 6 flagship journals January – June 2010. It provides a means of recalling to memory, in an evening or two, practical clinical points the editor considered applicable primary care.

The numbers in the brackets refer to the abstract. For example, [2-6] refers to the sixth article abstracted in February.

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 medical subject headings from ADVANCED DIRECTIVES to WEIGHT GAIN 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 Medicine*
- 4) The full abstracts may be accessed from the monthly issues on the website, 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

PRACTICAL CLINICAL POINTS JANUARY-JUNE 2010

Reminders of points of clinical interest and importance which primary care clinicians may wish to advise patients about, consider, and be aware of:

- 1-1 Vitamin D deficiency and insufficiency is common.. It has been linked to several common and morbid conditions. We have a way to go to prove causality.
- 1-2 Vitamin D alone may not be effective in preventing fracture; add calcium.
- 1-3 Weight gain experienced by a typical American must be caused by *repeated* changes in diet, physical activity, or both.
- 1-4 Antidepressant drug effects: there is little evidence to suggest they produce specific pharmacological benefit to the majority of patients with less severe acute depression.
- 1-5 Risk of cardiovascular disease and all cause mortality among patients with type-2 diabetes prescribed oral antidiabetes drugs: A cautionary note about sulfonylureas Pioglitazone outshines rosiglitazone. Metformin still a first-line drug.
- 1-6 The metabolic syndrome begins with excess central obesity.
- 1-7 Discussion of C-reactive protein as a risk marker. Do we need any more risk factors for primary prevention at this time?
- 1-8 Does treatment of hypertension prevent dementia?

- 2-1 An approach to urinary tract infection in primary care.
- 2-2 Both low and high HbA1c values are associated with increased mortality and cardiac events. in patients with type-2 diabetes.
- 2-3 Prognosis in patients with kidney disease associated with a given level of glomerular filtration rate varies substantially, based on the presence and severity of proteinuria.
- 2-4 There is no safe dose of tobacco smoke. Pipes and cigars have substantial nicotine content and cause measurable lung damage.
- 2-5 In persons with advanced cognitive impairment, feeding tubes do not improve survival, prevent aspiration, prevent decubitus ulcers, or improve other clinical outcomes.
- 2-6 Symptomatic superficial venous thrombosis is not benign. .It is a risk factor for deep vein thrombosis.
- 2-7 People with a history of depression are more likely to get the chronic fatigue syndrome, and vice-versa.

- 3-1 Aspirin is not effective in preventing CVD in patients with asymptomatic peripheral vascular disease. (Primary prevention) And bleeding rates are higher.

- 3-2 The metabolic syndrome does not provide better disease prediction than its individual components: (greater waist circumference, hypertriglyceridemia, hyperglycemia, hypertension, low LDL-cholesterol). The root cause is an unhealthy lifestyle. Because treatment strategies are available for the individual risk factors, rather than the MetS itself, it is not clear whether the diagnosis of MetS can improve treatment strategies.
- 3-3 Liraglutide, a newly approved glucagon-like peptide, may benefit patients who have inadequate diabetes control despite use of other antidiabetes therapy.
- 3-4 Higher HbA1c values in the normal range can identify increased risk of diabetes and cardiovascular complications.
- 3-5 Unequal leg length is a risk factor for osteoarthritis of the knee, which is potentially modifiable.
- 3-6 Vitamin D supplementation in the age of lost innocence “The effect of vitamin D supplements on cardiovascular disease, diabetes, and hypertension remains uncertain. However, the available evidence in favor of vitamin D supplementation is far more promising than for other vitamin or mineral supplements.”
- 3-8 23-valent pneumococcal vaccine is effective in preventing pneumonia and improving survival in nursing home residents.
- 4-1 Combined, four adverse behaviors decreased life expectancy by about 12 years: smoking, excess alcohol, lack of exercise, and little intake of fruits and vegetables.
- 4-2 As you age, regular moderate exercise is required to prevent weight gain.
- 4-3 For atrial fibrillation, lenient rate control (<110) is non-inferior to strict rate control (<80) in terms of major clinical events. This makes it easier for primary care.
- 4-4 Completing advanced directives and living wills is important. More than a quarter of elderly adults may need surrogate decision-making before death.
- 4-5 Commentary on driving fitness in elders with cognitive impairment--a problem for primary care clinicians.
- 4-6 What makes a good predictor for future cardiovascular disease? Should have a favorable risk-benefit ratio, reasonable cost, acceptability, and convenience.
- 4-7 Increased fructose and sucrose (caloric sweetener) intake is associated with dyslipidemia.
- 5-1 The cutpoint for HbA1c to diagnose diabetes varies with race/ethnicity.
- 5-2 Substituting whole grains, including brown rice for white rice, may lower risk of type-2 diabetes.
- 5-3 Nut consumption improves blood lipid levels in a dose-related manner.

- 5-4 Once-only flexible sigmoidoscopy screening significantly reduced incidence and mortality of colorectal cancer. Possibly a compromise intervention to reduce incidence of CRC.
- 5-5 Metformin induces vitamin B-12 malabsorption and low serum levels of B-12.
- 5-6 Pioglitazone and vitamin E are associated with improvement in nonalcoholic steatohepatitis.
-
- 6-1 QRISK2 score is validated to determine risk of future cardiovascular disease.
- 6-2 Unintended effects of statin drugs: cataracts, liver dysfunction, myopathy, and renal failure.
- 6-3 Dietary management is appropriate for all patients with hypertension. (Eg, the DASH diet)
Low salt, fish, poultry, nuts, legumes, low fat dairy, vegetable, fruit, whole grains, poly-unsaturated and mono-unsaturated fat (olive, canola, soybean, corn safflower, and sunflower oils)
Avoid red meat, full fat dairy, snacks and desserts high in sugar, white flour, butter, coconut oil, palm-kernel oil, sweetened beverages, candies, and cookies.
- 6-4 Maintaining optimal weight during middle age is important for prevention of diabetes.
- 6-5 Periodontal disease is a risk factor for cardiovascular disease. Encourage tooth-brushing.
- 6-6 Consider oseltamivir ring prophylaxis to contain and reduce transmission of influenza.

MEDICAL SUBJECT HEADINGS JANUARY - JUNE 2010

ADVANCED DIRECTIVES

ASPIRIN

ATRIAL FIBRILLATION

CARDIOVASCULAR DISEASE

CHRONIC FATIGUE SYNDROME

COGNITIVE IMPAIRMENT

COLORECTAL CANCER

C-REACTIVE PROTEIN

DEMENTIA

DEPRESSION

DIABETES

DRIVING FITNESS

DYSLIPIDEMIA

FEEDING TUBES

HEALTH BEHAVIORS

HUMAN GENOME

HYPERTENSION

INFLUENZA

KIDNEY FUNCTION

METABOLIC SYNDROME

MYOCARDIAL INFARCTION

NONALCOHOLIC STEATOHEPATITIS

NUTS

OBESITY

OSTEOARTHRITIS

PERIODONTAL DISEASE

PHYSICAL ACTIVITY

PNEUMONIA

QRISK2 RISK SCORE

RICE

RING PROPHYLAXIS

RISK PREDICTORS

SCREENING

SIGMOIDOSCOPY

STATIN DRUGS

SWEETENERS

TOBACCO

URINARY TRACT INFECTION

VASCULAR DISEASE

VENOUS THROMBOEMBOLISM

VITAMIN B-12

VITAMIN D

WEIGHT GAIN

ADVANCED DIRECTIVES

“More Than A Quarter Of Elderly Adults May Need Surrogate Decision-Making Before Death.”

4-4 ADVANCED DIRECTIVES AND OUTCOMES OF SURROGATE DECISION-MAKING BEFORE DEATH

Advanced directives (**AD**) document patients’ wishes; A living will (**LW**) documents wishes for life-sustaining treatment. They are designed to protect patient autonomy:

A durable power of attorney for health care (**DPAHC**) designates a surrogate decision-maker.

This study determined the prevalence and predictors of lost decision-making capacity, and care received at the end of life.

The study used data from the Health and Retirement Study, a biennial longitudinally representative cohort of older adults. The study was limited to persons age 60 and older who died between 2000 and 2006 for whom a reliable proxy was interviewed after the participant’s death.

Surrogate decision-making is often required for elderly Americans at the end of life. In this study 30% required decision-making and lacked the capacity to do so. “These findings suggest that more than a quarter of elderly adults may need surrogate decision-making before death.”

Among subjects who needed surrogate decision-making, 68% had an advanced directive. This is a great advance since 1994 when only 21% of seriously ill hospitalized patients had an AD. This suggests that many elderly find these documents familiar, available, and acceptable, and that they and their families think they have value.

For most subjects who had appointed a DPAHC, the surrogate’s decisions matched the choice of the subject.

“Although a causal relationship cannot be inferred, our findings suggest that advanced directives do influence decisions made at the end of life.”

“We suggest . . . that living wills have an important effect on care received and that a durable power of attorney for health care is necessary to account for unforeseen factors.” If a DPAHC is an extension of the patient, then surrogate decisions must be accepted as valid expressions of the patient’s autonomy.

Both a LW and a DPAHC appear to have a significant effect on the outcomes. Advanced directives are important tools for providing care in keeping with the patient’s wishes.

The health care system should ensure that medical providers have the time, space, and

reimbursement to conduct the time-consuming discussions required to plan appropriately for the end of life. Elderly patients are likely to welcome these discussions.

Conclusion: Patients who prepared ADs received care that was strongly associated with their preferences. These findings support the continued use of advanced directives.

It is a tragedy to live too long. More people (and more in the medical profession) are accepting death as a normal part of living. If there were no death, there would be no life. Very few persons now request that "everything be done".

Fortunately, we now have Hospice and Palliative Care to ease the transition. I can't say enough good about Hospice. Many people and their families, however, wait too long to request their help.

More persons are now completing ADs. We still have a way to go.

Elders: discuss this important part of health care with your family !

ASPIRIN

Marginal Benefits and Higher Rates of Bleeding.

3-1 ASPIRIN AS PREVENTIVE THERAPY IN PATIENTS WITH ASYMPTOMATIC VASCULAR DISEASE [Editorial]

Antiplatelet therapy has been a cornerstone of prevention and therapy. Strong data support aspirin in the setting of acute MI or stroke. In patients with suspected acute MI, early vascular mortality has been reduced by 23%. In stroke trials, low-dose aspirin was associated with a significant reduction in recurrent ischemic stroke and mortality. A meta-analysis of trials in patients with *symptomatic* stable CVD demonstrated a consistent association between aspirin and reduction of cardiovascular morbidity and mortality.

This issue of JAMA reports a double-blind randomized trial of aspirin in 3350 patients age 55-75 with screening-detected low ankle-brachial index in persons with no previous history of CVD events. Participants received: 1) aspirin 100 mg/d or 2) placebo for a mean of over 8 years. Aspirin was *no more* effective than placebo at reducing fatal or non-fatal coronary events, stroke, or revascularization, and had no significant effect on secondary endpoints.

Aspirin was associated with a statistically non-significant increase in major hemorrhage. (2% vs 1.2%; hazard ratio = 1.7). Intracranial hemorrhage (3 fatal) occurred in 11 patients in the aspirin group vs 7 in the placebo group.

Why does the available evidence suggest that aspirin has little benefit in reducing rates of cardiovascular events in primary prevention? The majority of participants in primary prevention trials were at low *absolute* risk of coronary disease. The annual risk of vascular events was only about 10% of that in high risk patients. Benefits of aspirin are more modest when used in primary prevention than when used for patients with established CVD.

Aspirin remains an effective therapeutic agent for *secondary* prevention.

Use of aspirin in primary prevention of CVD depends on physicians' judgment of benefit vs risk of bleeding in the individual patient. A history of MI or ischemic stroke will automatically place an individual at high risk, and is an indication for aspirin.

Aspirin has been routinely recommended for patients with diabetes. However, the individual risk of a vascular event varies widely. I believe not all patients with diabetes should be exposed to the risk of bleeding (eg, younger patients with short history of diabetes and no other risk factors). For older patients with diabetes, attention to other risk factors (BP, lipids, BMI) may be more productive than use of aspirin. The patient's' fully-informed preference also plays an important role.

ATRIAL FIBRILLATION

Lenient Rate Control Was Non-Inferior In Terms Of Major Clinical Events

4-3 LENIENT VERSUS STRICT RATE CONTROL IN PATIENTS WITH ATRIAL FIBRILLATION

Rate control (**RC**) is often the therapy of choice for atrial fibrillation (**AF**). Guidelines recommend strict rate control. But this is not based on clinical evidence.

This study hypothesized that lenient RC is not inferior to strict RC for preventing cardiovascular morbidity and mortality in patients with AF.

The prospective, multicenter, randomized, open-label, non-inferiority trial was designed to compare two rate control strategies in patients with permanent AF. All 614 subjects (mean age 68) had AF for at least 12 months, and a resting heart rate above 80.

During a dose-adjustment period, patients received one or more negative dromotropic drugs (beta-blocker, calcium channel blocker, or [rarely] digoxin) used alone or in various combinations until heart rate targets were achieved.

Patients assigned to lenient control had a target resting rate below 110. Those assigned to strict control had a target resting rate below 80, and a target rate of below 110 during moderate exercise.

Patients were followed-up periodically for at least 2 to a maximum of 3 years. Heart rate was determined at each visit and drugs adjusted if necessary.

Primary outcome = a composite of heart failure, stroke, systemic embolism, bleeding, life-threatening arrhythmic events, and death from cardiovascular causes.

Outcomes:	Lenient	Strict
Baseline heart rate (mean)	96	96
Mean heart rate at end of adjustment period	93	76
Mean heart rate at end of study	85	75

Target rate achieved at end of adjustment period	98%	67%
Required combination drug therapy	30%	69%
Composite primary outcome	13%	15%

Lenient rate control was non-inferior with regard to prevention of the primary outcome.

Adverse effects of drugs were low and similar between groups. Dizziness and fatigue were slightly less prevalent in the lenient group.

Conclusion: As compared with strict rate control, lenient rate control was non-inferior in terms of major clinical events over 3 years.

This certainly makes things simpler for the clinician as well as for the patients. It may be difficult in some patients to achieve strict control as defined by the study. Only 2/3 of study patients achieved this rate.

Three years may be too short a period to determine overall effects.

Judiciously lowering ventricular rate in individual patients, while determining symptom control, may be the way to go. As usual, rely on the patient to tell you the best rate.

CARDIOVASCULAR DISEASE

Higher HbA1c Values in the Normal Range Can Identify Increased Risk of Diabetes and Cardiovascular Complications

3-4 GLYCATED HEMOGLOBIN, DIABETES, AND CARDIOVASCULAR RISK IN NON-DIABETIC ADULTS

This study characterized and compared the relationships between glycosylated hemoglobin (**GH**; HbA1c) and fasting glucose and the risk of developing diabetes, coronary heart disease (**CHD**), ischemic stroke, and death from any cause in a large cohort of middle-aged community-dwelling adults.

Measured GH in over 11 000 adults at baseline (1990-1992). None had a history of diabetes or cardiovascular disease. Obtained blood for determination of GH.

Followed periodically for up to 15 years.

Baseline characteristics:

GH (%)	<5	5.0 to 5.4	5.5 to 5.9	6.0 to 6.4	6.5 and over
No. of persons	949	4950	3683	1031	479
Fasting glucose					
< 100 mg/dL (%)	61	53	33	14	1.7
100 to 125 (%)	39	45	64	67	28
126 & over (%)	0.8	1.1	3.0	18	71

BMI	26	27	28	30	32
During follow-up, the cumulative incidence of diabetes was 20%:					
	<5%	5.0 to 5.4	5.5 to 5.9	6.0 to 6.4	6.5 and over
Incidence (%)	6	12	21	44	79

Incidence rates per 1000 person-years rose steadily from about 5 in the lowest GH quintile to over 100 in the highest. Baseline GH of less than 5% was associated with approximately half the risk of development of diabetes as those with GH 5.0 to 5.4

There was an increasing risk of CHD, ischemic stroke, and death from any cause with higher levels of GH.

There was no evidence of a threshold value of GH for development of diabetes.

But for death from any cause, there was “J shaped” association. Those in the less than 5% group had a significantly higher death rate than those with GH 5.0 to 5.4. (Hazard ratio = 1.48)

“Our findings show that people with glycated hemoglobin value of 6% or higher are at high risk for development of diabetes, even after adjustment for other risk factors, and independently of baseline fasting glucose levels.”

GH is also a marker for cardiovascular risk and death even after accounting for baseline fasting glucose levels--“suggesting that glycated hemoglobin may be superior to fasting glucose for characterizing long-term risk”.

“Our data suggest that glycated hemoglobin values within the normal range can identify persons at increased risk of coronary heart disease, stroke and death before the diagnosis of diabetes.”

Conclusion: In this community-based population of non-diabetic adults, GH was associated with risk of diabetes, and risks of cardiovascular disease and death from any cause as compared with fasting glucose.

This is an interesting study. And I believe a helpful one.

Are we headed toward a more convenient and perhaps a less costly single test, which will offer a helpful prognosis before development of diabetes, as well as a diagnosis of diabetes?

(The ADA states that an HbA1c of 6.5% and over is diagnostic of diabetes.)

Will adding another risk factor lead patients to better lifestyles? A HbA1c of 6.0, indicating considerably increased risk, may induce some patients to adopt more healthful lifestyles.

The test must be done in a certified and standardized laboratory.

Less Frequent Tooth Brushing--More Periodontal Disease--Higher Risk of CVD

6-5 TOOTH BRUSHING, INFLAMMATION, AND RISK OF CARDIOVASCULAR DISEASE: RESULTS FROM A SCOTTISH HEALTH STUDY

There has been increasing interest in a possible link between dental disease, specifically periodontal disease (**PD**), and CVD. Inflammation plays an important link in the pathogenesis of atherosclerosis.

Poor oral hygiene is the major cause of PD, a chronic infection of the tissue surrounding the teeth. It is one of the most common chronic infections and is associated with a moderate systemic inflammatory response such as raised concentrations of C-reactive protein and other inflammatory markers.

This study examined whether self-reported tooth brushing behavior is associated with increased markers of inflammation and CVD.

The Scottish Health Study is a cross sectional survey of a nationally representative sample of the general population living in Scottish households.

Interviewers visited households and collected data on demographics, medical history, and health behaviors, including oral health. Oral health behavior was assessed from self-reported frequency of visits to a dentist, and tooth brushing (twice daily, once daily and less than once a day.)

The final sample size was 11 869

Linked the database to hospital admissions and deaths. Primary endpoint = composite of fatal and non-fatal CVD. There were 555 CVD events over an average of 8 years.

Poor oral hygiene habits were more prevalent in middle-aged men and were associated with other CVD risks such as smoking, obesity, and hypertension.

Model of tooth brushing and CVD:

Tooth brushing	Hazard ratio (adjusted for multiple possible confounders)\
Twice a day	1.00 (reference)
Once a day	1.3
< Once a day	1.7

There were significant associations between frequency of tooth brushing and markers of low grade inflammation. Levels of C-reactive protein rose from 3.07 mg/L to 4.18 mg/L as frequency of tooth brushing declined. Fibrinogen levels rose from 2.86 g/L to 2.98 g/L

In this study, participants who brushed their teeth less often had a 70% increase in risk of CVD events compared with frequent brushers.

Doctors should be alert to the possible oral source of an increased inflammatory burden.

Few studies use a proxy observation to link with a clinical endpoint.

While this study was not definitive, it was provocative. And, I believe, important clinically.

The strength of the study lies in the large study-group of representative individuals in the Scottish population. This increases generalizability

The advice regarding the importance of recognizing PD as a general health problem is worth while in itself. Primary care clinicians should include inspection of the mouth in the physical examination. And urge their patients (especially middle-aged males) to adopt good dental hygiene and regular visits to the dentist.

The study strengthens the association between PD and CVD, which has been noted for years.

1-5 “RISK OF CARDIOVASCULAR DISEASE AND ALL CAUSE MORTALITY AMONG PATIENTS WITH TYPE-2 DIABETES PRESCRIBED ORAL ANTIDIABETES DRUGS”

See under DIABETES

6-1 AN INDEPENDENT AND EXTERNAL VALIDATION OF QRISK2 CARDIOVASCULAR DISEASE RISK SCORE See under RISK SCORES

CHRONIC FATIGUE SYNDROME

“People With A History Of Depression Are More Likely To Get CFS, And Vice-Versa”

2-7 CHRONIC FATIGUE SYNDROME [Editorial]

This brief editorial suggests that depression and CFS are linked. The chief risk of CFS is suicide. These patients should be screened and treated for depression.

Clinical experience indicates that in patients with severe CFS, such programs may need to be adapted and prolonged, but that they can be the trigger for improvement and sometimes dramatic recovery. The alternative is no-treatment, which can be disastrous.

The editorialist does not suggest a proven causal relationship. I believe many patients with CFS are depressed.

Please read the full abstract.

COGNITIVE IMPAIRMENT

4-5 DRIVING FITNESS AND COGNITIVE IMPAIRMENT

As the population continues to age, society will be faced with increasing numbers of older drivers, some of whom may be cognitively impaired. Primary care physicians will increasingly face the need to assess risk and intervene.

But research has not yet determined the level of impairment that constitutes an unacceptable driving risk.

Many older individuals in the early stage of dementia can and do drive safely. At some point, as the disease progresses, however, they will need to stop driving. Physician's role in addressing the needs and safety of these patients and their community are challenging.

As evidence continues to evolve, it has become clear that the scope of responsibilities should be shared by physicians, other health care professionals, licensing agencies, and the community. They must identify cognitively impaired drivers who may pose a threat to public safety, but also ensure that the resources are in place to help these drivers manage the transition to driving retirement while maintaining their mobility in the community.

In my experience, primary care clinicians rarely face the ethical dilemma balancing patient confidentiality against public safety. When it occurs, it may be difficult. Enlisting the support of the family is essential.

There is no gold standard for determining driving fitness.

We may be able to avoid the decision by gentle persuasion, conversation, and counseling over several visits. This is preferable to abruptly giving the patient a prescription "Do not drive". Meanwhile the elderly patient may agree to limit driving to daytime in the local neighborhood.

Once a patient begins to lose his way while driving, has an automobile accident, experiences falls, and fails to meet the criteria of the instrumental activities of daily living, the decision to stop driving will be easier.

The patient and the family must be notified before the physician decides to notify the licensing authorities.

There are other reasons to recommend stopping driving; physical and visual disability, use of medications that may sedate and confuse.

I have a friend who, reluctant to stop driving, did so when her physician told her she would have no defense if she were in an accident. If sued, she might lose everything she had.

COLORECTAL CANCER

Significantly Reduced Incidence and Mortality from CRC

5-4 ONCE-ONLY FLEXIBLE SIGMOIDOSCOPY SCREENING IN PREVENTION OF COLORECTAL CANCER

Screening can potentially prevent CRC because most arise from adenomas, predominantly symptomless growths that develop in 20-30% of the population.

Two thirds of CRCs and adenomas are located in the rectum and sigmoid.

Flexible sigmoidoscopy (FS) is well accepted, safe, and quick. It may be a suitable method for population screening.

This randomized trial examined the hypothesis that only one FS screen between ages 55-64 is cost effective, acceptable, and reduces CRC incidence and mortality. This is based on observations suggesting that most people who develop a distal colon cancer will have developed an adenoma by age 60, and removal of adenomas by sigmoidoscopy offers protection against distal CRC.

The trial entered (1994-1999) 170 432 men and women, age 55-64 (mean age 60) from multiple centers in the UK. Those with a family history of CRC or symptoms of CRC were managed outside the trial because randomization would not have been in their interest.

Randomized (ratio of 1:2) to: 1) intervention group (offered a flexible sigmoidoscopy), or 2) controls (not contacted).

All adenomas were removed.

Those with adenomas larger than 10 cm, 3 or more adenomas, tubulovillous or severe dysplasia, or malignant disease were referred for colonoscopy.

Of the subjects actually screened, 95% were discharged because there were no polyps, or only low-risk polyps. 5% were referred for colonoscopy.

CRC incidence and mortality over a mean of 11 years:

A. Controls (n = 112 939)

Incidence of CRC	Cases	Rate per 100 000 person-years
Rectum and sigmoid	1192	98
Proximal	628	51
CRC mortality	538	44

B. Screened (n = 40 621)

Incidence of CRC	Cases	Rate per 100 000 person-years
Rectum and sigmoid	215	48
Proximal	224	50
CRC mortality	111	25

C. Hazard ratios (Screened vs controls)

Rectum and sigmoid	0.50
Proximal	0.97
CRC mortality	0.57

The estimated number of people needed to be screened to prevent one death due to CRC = 489.

There was a 43% reduction in death due to colorectal cancer in people who attended screening compared with controls.

There was no effect of screening on incidence of CRC in the proximal colon.

Economic analysis suggests that screening is cost-effective due to lower costs of treatment of CRC. Adequately trained nurses can undertake flexible sigmoidoscopy as competently as can Gastroenterologists. Public acceptance of nurse-led sigmoidoscopy screening is high.

Conclusion: Flexible sigmoidoscopy is a safe and practical test, and when offered only once to people between ages 55-64, confers a substantial and long-lasting protection from CRC.

Relatively few persons in the US undergo colonoscopy.

I believe FS is not a substitute for colonoscopy. It is an added screening procedure.

Since sigmoidoscopy requires less elaborate preparation, is more convenient, can be performed by health-care personnel other than gastroenterologists, many more patients may be willing to accept it.

Screening sigmoidoscopy may be repeated periodically and augmented with fecal occult blood testing. Costs to patients and to society will be much lower.

Many CRCs were discovered during the one and only screening sigmoidoscopy and were successfully treated.

C-REACTIVE PROTEIN

Do We Need Any More Risk Factors For Primary Prevention At This Time?

1-7 C-REACTIVE PROTEIN AND CARDIOVASCULAR RISK

Inflammation contributes to the pathogenesis of atherosclerosis. The inflammatory marker C-reactive protein (**CRP**) can be used to predict cardiovascular events.

This month, Lancet presents a comprehensive meta-analysis on these issues. The analysis consisted of over 50 prospective studies in over 160 000 persons. It included nearly 28 000 fatal and non-fatal disease outcomes.

CRP concentrations were linearly associated with most established risk factors. And with several other inflammatory markers, including fibrinogen and interleukin 6 (the biological mediator of hepatic CRP production.)

CRP concentrations were also strongly associated with coronary heart disease, ischemic stroke, vascular mortality, and non-vascular mortality. The association with cardiovascular outcomes was confounded considerably by established risk factors.

What is the role of CRP for *primary prevention*?

Opponents believe that CRP, compared with established risk factors, provides little improvement in risk prediction. Proponents have argued that CRP does help to reclassify relevant risk categories.

Does CRP have a *causal* role in the development of cardiovascular disease?

CRP might have biological effects on endothelial function, coagulation, fibrinolysis, oxidation of LDL, and plaque stability. However, several studies have reported a lack of concordance between CRP concentrations and cardiovascular risk. This is an argument against causality.

In the meta-analysis, associations between CRP concentrations and various cardiovascular outcomes were attenuated on adjustment for known risk factors. The investigators interpret this as an argument against causality.

Even if CRP turns out *not* to be causal, it might be useful to identify individuals at risk and to quantify the efficacy of interventions.

CRP has been a hot topic in the recent medical literature.

Do we need any more risk markers to guide primary prevention? In my view, we do not need any additional risk markers for primary care until we properly apply those we already know are established and valid. Thus far, we have failed miserably to do so.

DEMENTIA

“The Case Remains Open”

1-8 ANTIHYPERTENSIVE AGENTS AND PREVENTION OF DEMENTIA

Various studies have shown an association between mid-life hypertension (especially if untreated) and likelihood of developing dementia. This raises the possibility that antihypertension drugs might offer a form of prevention.

A prospective cohort study in this issue of BMJ reported the possible role of angiotensin receptor blocking (ARB) agents in reducing risk of dementia and in slowing its progression. The study followed over 800 000 male subjects older than age 65 with cardiovascular disease. and found significantly lower hazard ratios for incident dementia associated with ARBs than with the ACE inhibitor lisinopril (HR = 0.81) and with other cardiovascular drugs (HR = 0.76).

In patients with preexisting Alzheimer Disease (AD), ARBs were associated with a lower risk of admission to a nursing home.

Association does not prove causation.

Effects of combined ACE-inhibitors and ARB may be additive.

The public health implications of finding an effective way for preventing dementia are immense.

Further work is needed to verify the usefulness of antihypertensives in general and ARBs in particular

I abstracted this article as a provocative intervention to be aware of.

I will look for follow-ups.

We would expect some reduction in vascular dementia by control of BP.

2-5 HOSPITAL CHARACTERISTICS ASSOCIATED WITH FEEDING TUBE PLACEMENT IN NURSING HOME RESIDENTS WITH ADVANCED COGNITIVE IMPAIRMENT

See under FEEDING TUBES

DEPRESSION

“There Is Little Evidence To Suggest That ADM Produce Specific Pharmacological Benefit To The Majority Of Patients With Less Severe Acute Depression”

1-4 ANTIDEPRESSANT DRUG EFFECTS AND DEPRESSION SEVERITY: A Patient-Level Meta-analysis

The American Psychiatric Association rates the Hamilton Depression Rating Scale (**HDRS**) scores for severity of depression:

8-13 mild

14-18 moderate

19-22 severe

23 and above very severe

It is likely that many outpatients seeking treatment for depression have scores less than 22.

This meta-analysis estimated the relative benefit of antidepressant medications (**ADM**) vs placebo in patients with depression. It combined data from 6 large randomized, placebo-controlled trials of adult patients with a broad range of baseline symptom severity. The trials included patients with low as well as high HDRS--from the low teens to upper 30s.

Five trials included only patients with major depression (HDRS 20-24); one included only patients with minor depression (HDRS 14). Three trials used the tricyclic antidepressant imipramine (*Generic*); 3 used the selective serotonin reuptake inhibitor paroxetine (*Generic; Paxil; GSK*)

Duration = 6 to 11 weeks.

Differences between medication and placebo varied substantially as a function of baseline severity of depression. Among patients with HDRS score below 23 (this includes some of those classified as severe), differences in effect between medication and placebo were small.

Estimates of the magnitude of the superiority of medication over placebo increased with increases in baseline depression severity, and crossed the threshold defined by the National Institute for Clinical Excellence (NICE-UK) for a clinically significant difference at a baseline HDRS score of 25.

“True drug effects (an advantage of ADM over placebo) were nonexistent to negligible among depressed patients with mild, moderate, and even severe baseline symptoms.”

The authors estimated the number needed to treat (NNT) to produce a better outcome for one randomly selected depressed patient compared with placebo treatment:

Mild to moderate depression	16
Moderate depression	11
Severe depression	4

There is little evidence to suggest that ADMs produce specific pharmacological benefit to the majority of patients with less severe *acute* depression.

For patients with very severe depression, the benefit of medications over placebo is substantial.

How does this article apply to primary care medicine?

Depression is very common. Most patients with depression present to primary care and are treated in primary care.

Patients with severe depression should be referred if possible.

A. For diagnosis:

Many patients will self-diagnose depression.

Many primary care clinicians would depend on the 2-question screen:

- 1. During the past month how often have you been bothered by feeling down, depressed, or hopeless?*
- 2. During the past month have you often been bothered by little interest or pleasure in doing things?*
(This, of course, does not grade severity of the depression.)
- 3. For more detailed diagnostic tests, Google presents many references to the HDRS and the Beck depression scale. Self-scoring questionnaires are available.*

Some primary care clinicians may use these.

B. For treatment:

I believe primary care clinicians would be liberal in prescribing ADMs. (Indeed, the NNT of 16 is not higher than for many other drugs.) They would likely not inform the patient that her depression is not severe enough to warrant prescription drugs.

Many patients with depression (including mild depression) are aware of drug treatments, and will request medication. (A tribute to the marketing ability of drug companies.) I believe most clinicians would comply with such requests.

The article did not deal with chronic depression.

Medicalization is prevalent in our society. Many patients will seek treatment for ills that are part of the normal ups and downs of living. "A pill for every ill." --whether or not the "ill" is really a disease. I believe medication for depression is overused.

DIABETES

A Cautionary Note About Sulfonylureas Pioglitazone Outshines Rosiglitazone Metformin Still A First-Line Drug

1-5 RISK OF CARDIOVASCULAR DISEASE AND ALL CAUSE MORTALITY AMONG PATIENTS WITH TYPE-2 DIABETES PRESCRIBED ORAL ANTIDIABETES DRUGS

This phase IV retrospective cohort study investigated the risk of myocardial infarction (**MI**), congestive heart failure (**CHF**), and all-cause mortality (**ACM**) associated with different classes of antidiabetes drugs in a large general practice database in the UK.

The study comprised clinical and prescribing data based on clinical records of about 5 million people. Obtained data on patients (n = 91 521) age 35-90 (mean age = 65) with an episode of drug care for DM-2 from 1990 to 2005. Identified oral antidiabetes drugs in individual patients from prescription records. Drugs were identified as used alone or in combination.

Used intervals of drug treatment as the unit of observation, defined as the period from onset of a drug treatment to onset of the next drug treatment, until censored, or until occurrence of the event of interest. There were a total of over 2.8 million intervals of treatment.

Compared the risks associated with each drug or drug combination with metformin monotherapy. (Metformin is advocated as first-line therapy.) Patients using insulin were excluded.

Mean follow-up per individual was 7 years. During the study period there were: 3588 first events of MI, 6900 first events of CHF, 18 548 ACM.

Metformin monotherapy was the most commonly prescribed drug (75%) followed by second generation sulfonylurea monotherapy (64%)

Hazard ratios compared with metformin alone

	MI	CHF	ACM
Second generation sulfonylureas	1.31*	1.39*	1.55*
Rosiglitazone (combined)	1.08	1.31*	0.80*
Pioglitazone (alone & combined)	0.78	1.18	0.61*
Rosiglitazone vs pioglitazone	1.34	1.05	1.41*

(* significant)

“Our study of observational data in general practice allows assessment of the relative benefits and hazards of use of oral antidiabetes drugs in a ‘real world’ clinical setting.”

The study extends the evidence, suggesting higher mortality with sulfonylurea use than metformin among unselected patients attending general practice.

In this study, there was no evidence of excess MI associated with thiazolidinediones. Mortality associated with pioglitazone was lower than with rosiglitazone.

Conclusions

1. The finding of a relatively unfavorable risk profile of sulfonylureas vs metformin for all outcomes examined are consistent with ADA recommendations that favor metformin as the initial treatment of DM-2.
2. The previous reports of an excess risk of MI associated with rosiglitazone compared with metformin were not confirmed.
3. Pioglitazone was associated with reduced all-cause mortality and a favorable risk profile compared with rosiglitazone.

This study is much more complex than I have outlined. I congratulate the investigators on their persistence in digging through such a mass of data.

The investigators calculated the data by 3 models using different possible confounding variables. I have reported only #1.

For primary care the message is: Be guarded about use of sulfonylureas. Use pioglitazone instead of rosiglitazone. Metformin is still a standard first drug.

Low And High HbA1c Values Were Associated With Increased Mortality And Cardiac Events.

2-2 SURVIVAL AS A FUNCTION OF HbA1c IN PEOPLE WITH TYPE 2 DIABETES

This retrospective cohort study assessed the association between all-cause mortality and HbA1c levels in patients with type-2 diabetes (**DM-2**) in a primary care setting.

Identified 2 cohorts of elderly patients who had a diagnosis of DM-2, whose treatment included oral drugs and insulin. All had their treatment intensified before baseline:

- 1) Over 27 000 patients whose treatment had been intensified from oral mono-therapy to combinations of oral drugs. (metformin + sulfonylureas)
- 2) Over 20 000 who had changed regimens to include insulin.

Primary outcome = all-cause mortality. Mean follow-up = 5 years.

Cohort 2 (n > 20 000; insulin intensified)

	1	2	3	4	5	6	7	8	9	10
HbA1c*	6.38	6.95	7.28	7.55	7.83	8.11	8.45	8.87	9.42	10.56
HR**	1.79	1.45	1.35	1.00	0.98	1.15	1.21	1.21	1.46	1.80

(* Mean HbA1c divided into deciles. Decile 4 = referent **Hazard ratio of all-cause death..)

HR fell between decile 1 and decile 4; then rose between decile 4 and decile 10 in a “U” shaped manner.

Consistent with all-cause mortality, insulin treatment was associated with an increased likelihood of progression to a first large-vessel disease event.

Cohort 1 (oral drug intensification with metformin + sulfonylurea) followed same “U” shaped path, but with lower mortality rates than cohort 2. The lowest mortality was at HbA1c of 7.5%. The U shape was much flatter, with only deciles 1, 9, and 10 varying much from referent.

“We have shown that an HbA1c of approximately 7.5% was associated with the lowest all-cause mortality and lowest progression to large-vessel disease.”

Decreased survival in patients achieving low mean HbA1c might be related to hypoglycemia, a common complication of intensive control. In this study, mortality was 3 times higher in patients who had severe hypoglycemia.

Lower survival reported in the group given insulin could suggest that insulin might heighten mortality risk.

“These data imply, for oral combination therapy, that a wide HbA1c range is safe with respect to all-cause mortality and large vessel events, but for insulin therapy a more narrow range might be desirable.”

This does not mean that there is no value in achievement of present glycemic targets for *micro*-vascular disease.

Conclusion: Low and high HbA1c values were associated with increased all-cause mortality and cardiac events.

This applies to a subset of patients with type-2 diabetes--the elderly and those who have established CVD or who are at high risk. We should treat these patients conservatively. For younger patients, more aggressive A1C lowering may be reasonable

Does elevated blood glucose per se lead to increasing development of atherosclerosis? Ie, if the patient had no dyslipidemia, had a normal BP and BMI, did not smoke, exercised regularly, and had no family history of CVD or other risk factors, would continuing hyperglycemia lead to atherosclerosis? I believe so. It might take longer.

Control of glycemia at a younger age would then create a legacy effect, lowering the risk of atherosclerosis as the years progress.

Would the new insulin sensitizers, which lower A1C without risk of hypoglycemia, offer any advantage? There is little to gain by strict glucose control later in life.

“May Benefit Patients Who Have Inadequate Control Despite Use Of Other Antidiabetes Therapy”

3-3 WEIGHING RISKS AND BENEFITS OF LIRAGLUTIDE: The FDA’s Review of a New Anti-diabetic Therapy

New therapies are needed to achieve glycemic goals because beta-cell function declines over time in patients with diabetes.

On January 25, 2010, The FDA approved liraglutide, a glucagon-like-peptide (GLP) for treatment of type-2 diabetes (DM-2) . The drug is given once daily by s.c. injection to improve glycemic control in adults.

In clinical trials, liraglutide resulted in reductions in the mean glycated hemoglobin (HbA1c) of 0.8 to 1.4 percentage points as compared with placebo. Compared as monotherapy with a sulfonylurea, liraglutide was associated with a lower risk of hypoglycemia. There was also greater weight loss and an absence of need to adjust the dose for patients with renal impairment.

There are potential serious safety concerns: In rodents, liraglutide was associated with increased risk of thyroid C-cell focal hyperplasia and C-cell tumors. The relevance to humans is not known. The FDA concluded that there is a low risk for humans, but did require additional studies in animals and establishment of a cancer registry to monitor the annual incidence of medullary cancer over the next 15 years. There is a possible increased risk of pancreatitis attributable to drugs that act through the GLP-1 pathway. The FDA requires a post-approval study to rule out any cardiovascular disease risks.

A. Incretins are a group of natural gastrointestinal peptide hormones released from the small bowel in

response to presence of nutrients. They have a number of actions, which improve blood glucose control:

Increase insulin secretion from the pancreas in a glucose-dependent manner

Decrease glucagon secretion from the alpha cells of the pancreas further reducing blood glucose

Inhibit acid secretion in the stomach and gastric emptying

May produce weight loss by increasing satiety, and decreasing food intake.

- B. Glucagon-like peptide-1 (GLP-1) is a natural incretin. It is rapidly inactivated by the enzyme dipeptidyl peptidase. It has a half-life of less than 2 minutes. It is not useful clinically. (Termed “glucagon-like” not because GLP-1 has glucagon activity--quite the opposite. The term comes from the proglucagon gene. GLP-1 is derived from the transcription product of that gene.)*
- C. Liraglutide (Victoza; Novo Nordisk) is a GLP-1 receptor agonist, an analogue of native GLP-1 with a fatty acid attached. A single daily subcutaneous injection provides action for about 12 hours. It improves control of blood glucose by the same mechanisms as natural incretins. It acts in a glucose-dependent manner--ie, stimulating insulin secretion only when blood glucose is higher than normal. It has negligible risk of hypoglycemia.. It leads to a lowering of triglyceride levels. It can be used alone, or in combination with other anti-diabetes drugs. Hypoglycemia is rare, but may result when used with sulfonylureas. It is not approved for use with insulin. It reduces HbA1c by about 1%. The most common adverse effects are gastrointestinal. It is expensive. One daily injection of 1.8 mg costs over \$800.00 a month.*
- D. Exenatide (Byetta; Amylin; Lilly) is also a GLP-1 analogue--a 39 amino acid peptide with a 50% amino acid homology with GLP-1. It is a synthetic version of exendin-4, a hormone found in the saliva of the Gila monster. It has biological properties similar to human GLP-1. Its half-life is much longer than half-life of GLP-1, but shorter than liraglutide. It must be given s.c. twice a day before meals. It is used at times as primary monotherapy and as adjunctive therapy combined with other anti-diabetes drugs.*
- E. Sitagliptin (Januvia; Merck) is a dipeptidyl peptidase inhibitor. It prolongs the half-life of native GLP-1. It may be used alone or in combination with other anti-diabetes drugs. It is given by mouth. Adverse effects are rare. As usual, we will not know all possible important adverse effects for some years.*

Both Have Advantages And Disadvantages. Patient Preferences Play An Important Part In Selection.

4-8 LIRAGLUTIDE VERSUS SITAGLIPTIN FOR PATIENTS WITH TYPE 2 DIABETES WHO DID NOT HAVE ADEQUATE GLYCEMIC CONTROL WITH METFORMIN

Incretins are peptide hormones normally secreted by the small bowel in response to presence of nutrients. They augment glucose-dependent insulin secretion, suppress glucagon secretion, delay gastric emptying and decrease food intake.

Incretins are inactivated rapidly by a peptidase. Their half life is in minutes.

Pharmacologic analogues to incretins (eg liraglutide; *Victoza*; Novo Nordisk) have been developed. They activate the incretin receptor. They resist degradation by peptidase. Thus, their half life is much longer.

Another pharmacological agent (sitagliptin; *Januvia*; Merck) acts by inhibiting the peptidase thereby prolonging the action of normally secreted incretins.

This study was done in 158 office-based sites in multiple countries. Subjects (n = 665) were patients with DM-2 who had been taking metformin (1500 mg or more daily) for 3 months or longer and had inadequate response--HbA1c 7.5% to 10%. Randomized subjects to: 1) 1.2 mg subcutaneous liraglutide daily, 2) 1.8 mg liraglutide daily, and 3) sitagliptin 100 mg orally daily. Baseline metformin dose remained stable in all subjects

Baseline demographics (means)

Age	55
BMI	32
HbA1c	8.5%

HbA1c reductions at 26 weeks (%)

Liraglutide 1.2 mg	-1.23
Liraglutide 1.8 mg	-1.50
Sitagliptin 100 mg	-0.90

Significantly more patients achieved HbA1c targets of < 7% with liraglutide than with sitagliptin.

Mean loss of bodyweight at 26 weeks was greater with liraglutide: -3.4 kg for 1.8 liraglutide and -1.0 kg for sitagliptin..

Minor hypoglycemia occurred in 5% of all 3 groups.

Nausea was troublesome in about 27% of the 1.8 mg liraglutide subjects, but over 24 weeks prevalence decreased to the low prevalence associated with sitagliptin. 7% of liraglutide patients withdrew vs 3% in the sitagliptin group.

Conclusion: Liraglutide, added to metformin, was superior to sitagliptin for reduction of HcbA1c, with a minimum risk of hypoglycemia.

At present, this is not a practical point for primary care. The drugs are too expensive. Many patients cannot afford them. Victoza is not available in many pharmacies now. As prices come down, and the drugs become more available, they may be useful.

Note the BMI. Almost all subjects were obese. A weight loss of 7 pounds would not help much.

Both have advantages and disadvantages. As usual, patient preferences will play an important part in selection.

5-1 GLYCATED HAEMOGLOBIN FOR DIAGNOSIS OF DIABETES IN CHINESE POPULATION

Substantial evidence shows that HbA1c is a useful tool for diagnosis of diabetes. Recently, an international expert committee with members of the American Diabetes Association, the European Association for the Study of Diabetes and the International Diabetes Federation noted that a level of 6.5% is sufficiently sensitive and specific to identify people who are at risk of developing retinopathy and who therefore should be diagnosed as having diabetes.

This cross sectional epidemiological survey evaluated the efficiency of HbA1c in diagnosing diabetes and identified the optimal threshold in an adult Chinese population.

Apparently healthy Chinese (n = 4886) age 20-79 (median = 50) participated in this cross sectional epidemiological survey. An oral 75 g glucose tolerance test (the “gold standard”) was done in all participants. The dataset included 3748 people with normal glucose tolerance, and 301 with diabetes.

Constructed a receiver operating characteristic curve (**ROC**), using thresholds 1, 2, 3, and 4 standard deviations of HbA1c (0.4%) above the mean of 5.5%. The corresponding HbA1c levels were: 5.9%, 6.3%, 6.7%, and 7.1%. The area under the ROC curve (0.865) represented the diagnostic accuracy of HbA1c alone for detecting undiagnosed diabetes.

With the ROC curve, determined the best trade-off between true positive tests and false positive tests. (Perfect trade-off would be 100% true positives and 0% false positives, indicated by the upper left corner of the graph)

Of all 4 HbA1c levels, a HbA1c of 6.3% represented the best trade-off. (Ie, the closest distance to the upper left corner of the ROC curve.)

Sensitivity and specificity for detecting diabetes:

HbA1c (%)	True positive (%)	False positive (%)
-----------	-------------------	--------------------

5.9	78	22
6.3	63	4
6.5	51	2.0 (US standard)
6.7	38	1
7.1	26	0.2
FPG		
126 and above	57	0

When the diagnosis of diabetes was confirmed by a glucose tolerance test, only 63% of patients with diabetes were correctly diagnosed by the HbA1c of 6.3%.

When the diagnosis of diabetes was confirmed by a glucose tolerance test, only 57% of patients with diabetes were correctly diagnosed by fasting plasma glucose of 126 or more. .

Conclusion: “HbA1c threshold of 6.3% was highly specific for detecting undiagnosed diabetes in Chinese adults, and had sensitivity similar to that of using a fasting plasma glucose of 7.0 mmol/L.” (126 mg/dL)

This is a long and complex study. I abstracted it with difficulty and in detail, at risk of causing confusion, not because of its specific application to ethnic groups. It describes the difficulty we have in diagnosing diabetes when the marginal cut-off points are approached.

It is easy to diagnose diabetes when the blood glucose is very high. (Years ago we depended on symptoms of excessive thirst, urination, unexplained weight loss, and glycosuria.) A very high spot blood glucose and a very high HbA1c will also diagnose diabetes. A very low spot blood glucose and a very low HbA1c will rule it out.

It is likely that a high HbA1c (Ie, 7.5%) will lead to more organ damage than 6.5% and a non-diagnostic level of 6.4% will cause some organ damage.

A problem arises as the cut points reach equivocal levels. If we inform a patient she does not have diabetes based on a HbA1c of 6.4% (vs the US cut-off point of 6.5%) we may miss the diagnosis. She may have a reasonable chance of actually having diabetes. The same goes for a fasting plasma glucose of 125.

I believe it is prudent to inform patients who have borderline cut-points that they have impaired sugar metabolism, strongly advise lifestyle changes and inform them that the disturbance will be reversed if diet, weight, and exercise are improved.

Labeling patients with a life-time diagnosis of diabetes may be harmful.

The important point about the level of HbA1c: Is it high enough to cause or accelerate organ damage (kidney, retina, nerve, heart)? Younger patients who have borderline cut-off levels of HbA1c will benefit more over the years with better glucose control. Older patients have less to gain. Strict drug control of a marginally high HbA1c and a marginally high fasting plasma glucose may cause more harm than benefit.

Of course, symptomatic disease should be treated aggressively.

So, what is diabetes? Diabetes is a disease in which metabolism of glucose is disturbed and causes blood glucose levels to rise high enough and last long enough to cause or accelerate organ disease.

Substitution of Whole Grains, Including Brown Rice for White Rice, May Lower Risk Of DM-2

5-2 WHITE RICE, BROWN RICE, AND RISK OF TYPE-2 DIABETES IN US MEN AND WOMEN

Rice has been a staple food for centuries. By the 20th century, the advance of grain-processing technology made large-scale production of refined grains possible. Through the refining process, the outer bran and germ portions of the intact rice grains (brown rice) are removed to produce white rice that primarily consists of starchy endosperm.

Consumption of white rice generates a stronger postprandial blood glucose response as measured by the glycemic index (**GI**)¹ than the same amount of brown rice. A systematic review (1999) found that the mean GI was 64 for white rice, and 55 for brown rice compared with 100 for glucose.

Higher GI has been consistently associated with elevated risk of type-2 diabetes (**DM-2**)

This study evaluated white and brown rice consumption in relation to DM-2

Prospectively ascertained diet and lifestyle practices and disease status among 39 765 men and 157 463 women in the Health Professionals Follow-up Study and two Nurses Health Studies 1984-2008. Subjects answered food frequency questionnaires at baseline and periodically.

Documented 10 505 incident cases of DM-2. (Follow-up = 20 and 22 years.)

Participants who ate at least 5 servings of white rice per week had 17% higher risk of developing DM-2 compared with those in the lowest category of intake of white rice.

There was a monotonically decreasing risk of DM-2 associated with increasing consumption of whole grains, including brown rice. In comparison with the lowest quintile of whole grain intake, the relative risk (**RR**) for the highest quintile was 0.73.

The replacement of 50 g of white rice (1/3 serving) per day with the same amount of brown rice was associated with lower risk. (**RR** = 0.84). When replacing 50 g of white rice per day with the same amount of whole grains, the **RR** was 0.64.

“In these 3 prospective studies of US men and women, we found that regular consumption of white rice was associated with higher risk of DM-2, whereas, brown rice was associated with lower risk.”

The current dietary guidelines identify grains, including rice, as one of the primary sources of carbohydrate intake, and recommends that at least half of carbohydrate intake come from whole grains.

Conclusion: Substitution of whole grains, including brown rice for white rice, may lower risk of DM-2. More carbohydrate intake should come from whole grains rather than from refined grains to prevent DM-2.

A healthy lifestyle includes a low glycemic load (GL) diet. This is best achieved by consuming low glycemic index foods in moderation.

The rapid blood glucose response to a high GL meal results in high insulin production. Over time, the excessive insulin-secretion of the pancreas may be impaired, leading to type-2 diabetes.

The blood glucose rise after a high GL meal causes increased insulin secretion, and leads to a reactive hypo-glycemia, increasing hunger and additional food intake. Obesity results. Low GL diets may lead to weight loss.

High GL are also associated with increased serum triglycerides, and decreased HDL-cholesterol and increased risk of cardiovascular disease.

Low GI foods and low GL diets improve the overall blood glucose response and better control of DM-2

Source: Linus Pauling Institute, Oregon State University,

Metformin Induces B-12 Malabsorption and Low Serum Levels

5-5 LONG TERM TREATMENT WITH METFORMIN IN PATIENTS WITH TYPE-2 DIABETES AND RISK OF VITAMIN B-12 DEFICIENCY

This placebo-controlled trial examined the long-term effects of metformin on serum concentrations of B-12, folate, and homocysteine in patients with type-2 diabetes (**DM-2**).

The trial included 390 outpatients with DM-2, aged 30-80. All patients were receiving insulin. Patients were randomized to: 1) insulin + metformin 850 mg 3 times per day, or 2) insulin + placebo 3 times per day.

Serum levels of B-12, folate, and homocysteine were checked at 4, 17, 30, 42, and 52 months.

Defined deficiency of B-12 as below 150 pmol/L, and low levels as between 150 and 220 pmol/L.

Over the 52 weeks, mean B-12 in the placebo group remained stable. In the metformin group, mean

levels fell in 4 months from a mean of 355 pmol/L to 300 pmol/L. Over the remainder of the study, mean B-12 levels continued to fall in the metformin group to about 280.

Change at 52 weeks:	Placebo	Metformin
B-12 concentration (pmol/L)	+ 0.2 (0%)	- 90 (- 19%)
Folate (nmol/L)	+ 1.01	+ 0.21 (Not statistically significant)
Homocysteine (umol/L)	+ 1.60	+ 3.28
At the end of the study:		
Deficiency of B-12 (%)	3	10
Number needed to be treated (NNH) to cause deficiency		14
Hazard ratio for B-12 deficiency caused by metformin (vs placebo)		5.5
Low level of B-12 (%)	7	18
Homocysteine levels (umol/L)	18	22

Metformin significantly reduced concentrations of B-12. The decrease persisted and grew over time.

The finding of a decrease in B-12 during metformin treatment is not a novel finding. That the decrease is progressive is novel. Concentrations in some patients drop to the level at which most authorities agree that substitution is required.

Metformin is thought to induce malabsorption of B-12 and intrinsic factor in the ileum, an effect that can be reversed by increased calcium intake.

Treatment of B-12 deficiency is relatively easy, cheap, safe, and effective, in effect arguing in favor of treatment on the basis that treatment can do no harm. However, there is no consensus on the issue of whether “asymptomatic” deficiency should be treated.

It is reasonable to assume that harm will eventually occur in some patients with metformin-induced B-12 deficiency.

Conclusion: In patients with DM-2 treated with insulin, those additionally treated with metformin had a seven percentage point greater absolute risk of B-12 deficiency than those treated with placebo during a 4.3 year follow-up. “Our data provide a strong case for routine assessment of vitamin B-12 levels during long-term treatment with metformin.”

The authors do not mention any clinical manifestations of B-12 deficiency even though 10% of subjects taking metformin developed deficient levels.

Why does calcium reverse malabsorption?

Since metformin is used so frequently in primary care, how should the primary care clinician respond to this study? I believe it prudent to advise these patients to take a multivitamin tablet daily. This supplies the recommended daily value of B-12 (6 mcg) as well as vitamin D (400 IU) and others. It will cost 3 to 4 cents daily. It would be reasonable to take the vitamin between meals to avoid competition with metformin. And take a calcium supplement.

Importance Of Maintaining Optimal Weight During Middle Age For Prevention Of Diabetes

6-4 ASSOCIATION BETWEEN ADIPOSITY IN MIDLIFE AND OLDER AGE AND RISK OF DIABETES IN OLDER ADULTS.

This prospective population-based cohort study of older adults examined the relationship between measures of overall body fat, body fat distribution, changes in these measures, and risk of DM-2 in older adults.

Entered (1989-1990), a group of 5201 ambulatory, non-institutionalized men and women age 65 and older (mean = 73). After exclusions for diabetes and other reasons, a cohort of 4193 remained.

At baseline and periodically thereafter, collected comprehensive information on health-related variables. Self-reported body weight at age 50 was collected at baseline.

Periodically determined height, body weight, and waist circumference (**WC**).

Calculated body mass index (**BMI**) from the self-reported weight at age 50 and the measured height at baseline. Determined BMI at baseline from measured weight and height. Classified participants as having DM-2 if fasting glucose was 126 mg/dL and above.

Over a median follow-up of 12 years, 339 new cases of DM-2 occurred among 4193 participants.

BMI at baseline, BMI at age 50, and waist circumference were strongly related to risk of developing DM-2.

Association between baseline measures of adiposity and risk of incident DM-2 in men 1989-2007.:

BMI quintiles	<23.3	23.3 - 25.0	26.1 - 26.6	26.7 - 28.6	>28.6
Hazard ratio (HR) for DM-2	1.00	1.9	2.9	4.4	5.6
Waist circumference (cm)	< 89.1	89.1 - 94.0	94.1 - 99.0	99.1 - 104.5	>104.5
HR for DM-2	1.00	2.1	2.2	3.9	5.1

(Ie, men with higher BMI and WC at baseline were much more likely to develop DM-2.

Women had similar associations)

Participants in the highest category of adiposity had approximately 2- to 6- fold increased

risk of developing DM-2 compared with those in the lowest category.

“We found that measures of overall and central adiposity were strongly associated with the risk of incidental diabetes in both men and women.” Weight gain during midlife (after age 50) and in late life (after age 65) is an important risk factor for diabetes among older adults.

It is possible that regional fat distribution is more important in the etiology of diabetes than absolute fat mass. Visceral fat and thigh fat are associated with impaired glucose tolerance and diabetes in older adults independent of total adiposity.

This analysis showed an association between waist circumference and diabetes risk in individuals with a BMI less than 25, suggesting that measurement of waist circumference may add important information beyond BMI regarding diabetes risk in normal weight individuals.

Conclusion: Among older adults, overall and central adiposity, and weight gain during middle age and after age 65 were associated with increased risk of diabetes.

The study emphasizes importance of:

- 1. Entering late middle-age with a normal BMI and waist circumference.*
- 2. Controlling weight and waist circumference before age 50, and after ages 50 and 65.*
- 3. Controlling waist circumference at any age, including individuals with BMI below 25.*

These risk factors apply to cardiovascular disease and hypertension as well.

3-4 GLYCATED HEMOGLOBIN, DIABETES, AND CARDIOVASCULAR RISK IN NON-DIABETIC ADULTS See under **CARDIOVASCULAR DISEASE**

DRIVING FITNESS

4-5 DRIVING FITNESS AND COGNITIVE IMPAIRMENT

See under **COGNITIVE IMPAIRMENT**

DYSLIPIDEMIA

Increased Fructose and Sucrose Intake is Associated with Dyslipidemia

4-7 CALORIC SWEETENER CONSUMPTION AND DYSLIPIDEMIA AMONG US ADULTS

In the US, total consumption of sugar has increased substantially in recent decades largely due to an increased intake of “added sugars”, defined as caloric sweeteners used by the food industry and consumers as ingredients of processed and prepared foods. Today, the most commonly added sugars are refined beet or cane sugar (sucrose) and high fructose corn syrup.

This study assessed the association between consumption of added sugars and lipid levels in US adults.

The cross-sectional study among non-institutionalized US adults (n = 6113; half women, half men) assessed data from the National Health and Nutrition Examination Survey (NHANES) 1999-2006. The study obtained nationally representative estimates of diet and health indicators.

Determined nutrient content of foods consumed by use of US Department of Agriculture National Nutritional Database and the My Pyramid Equivalents Database. Added sugars were determined from 337 different foods.

Determined the intake of added sugars for each respondent, and the % of energy intake (kcal) from added sugars.

The mean of self reported weight gain was 2.8 pounds among those with 25% or greater total energy from added sugars compared with a mean loss of 0.3 pounds among those whose total intake of added sugars was less than 5%.

Total energy intake increased as the proportion of energy from added sugars increased from 5% of total energy to 25% or greater.

Outcomes (means)	% of added sugars	
	5%	25%
HDL (mg/dL)	59	48
TG	105	114
TG/HDL	2.4	3.1
LDL (women)	116	122 (Estimates from fig 3 p 1495)
(men)	No difference	

(The authors offer no explanation for this..)

Odds ratios	% of added sugars	
	5%	25%
Low HDL	1.00	3.1 (< 40 mg/dL men; < 50 women)
High TG (150)	1.00	1.2
High LDL (>130)	1.00	1.2
High TG/HDL (>3.8)	1.00	1.6 (Estimated from a model adjusting for multiple possible confounding factors.)

Individuals in this study consumed an average of about 16% (one sixth) of their daily calories from added sugars. This represents a substantial increase from 1977 when added sugars contributed only about 11% of the calories consumed by adults.

“Our results support the importance of dietary guidelines that encourage consumers to limit their intake of added sugars.”

Conclusion: Higher consumption of added sugars was associated with several important measures of dyslipidemia. The data support dietary guidelines that target a reduction in consumption of added sugar.

Improves Blood Lipid Levels in A Dose-Related Manner

5-3 NUT CONSUMPTION AND BLOOD LIPID LEVELS

Nuts are rich in plant protein and fat, mostly unsaturated fat. They are a rich source of additional nutrients: dietary fiber, minerals and vitamins, as well as antioxidants and phytosterols.

Epidemiological studies consistently show that frequent nut consumption lowers risk of CHD--up to 37% lower in subjects who consume 4 or more servings of nuts per week, compared with those who seldom eat nuts.

In 2003, the US Food and Drug Administration issued a qualified statement that eating 1.5 oz of almonds, cashews, hazelnuts, macadamias, pecans, pistachios, walnuts, pine nuts, hazelnuts, or peanuts may reduce CHD risk.

This comprehensive MEDLINE search (1992-2004) identified 25 nut-consumption trials in which the dietary intervention was exclusively nuts.

Effects of nut consumption were similar in men and women, across all age groups, and were independent of the specific type of nut consumed.

Estimated changes from baseline (nut consumers vs controls):

A.	mg/dL	% change	
Total-c	- 11	-5	
LDL-c	- 11	-7	(Overall)
< 130	- 4		
130-160	-10		
>160	-18		(Greater effect in persons with higher LDL)
HDL-c	+0.1	+0.2	(Essentially no change in HDL)
TG	- 3.1		(Overall)
< 150	-1.0		
> 150	-21		(Greater effect in persons with higher TG)

B. Changes varied with baseline body mass index (BMI)

BMI	Total-c	LDL-c	TG
< 25	-12%	-12%	-6%

25-30	- 11	-9	-1	
>30	-9	-7	-2	(As BMI increased, benefits decreased.)

The estimated effects of nut consumption on lipids were dose-related:

At 20% energy from nuts

2.5 oz in a 2000 kcal diet: - 4.5% for TG and - 6.5% for LDL-c

At 12% of energy from nuts

1.5 oz in a 2000 kcal diet: -3, .2% for TG and - 4.9% for LDL-c

(1.5 oz is recommended by the US Food and Drug Administration.)

The cholesterol-lowering effects of nut consumption are dose-related and are most pronounced in subjects with higher baseline LDL-c or lower BMI.

Nuts lowered TG in subjects with hypertriglyceridemia, and also lowered the ratio of LDL-c to HDL-c and the ratio of TG to HDL-c.

The estimated overall reduction in LDL-c (7 %) is modest compared with the effects of statins. The effect of frequent nut consumption is likely due to other factors as well. Epidemiological studies have reported a summary 37% reduction in risk of CHD, which is double that attributable to lowering LDL-c by 7%. Other beneficial effects of nuts include improved endothelial function, and lowering lipoprotein (a) levels. In addition, nut consumption is associated with a lower risk of developing type-2 diabetes.

Conclusion: Nut consumption improves blood lipid levels in a dose-related manner, particularly among subjects with higher LDL-c or with lower BMI.

Remarkably, peanuts have nutrients similar to tree nuts. Peanuts and peanut butter are universally available, are less expensive than other nuts, and are a convenient, delicious snack.

According to the US Dept. of Agriculture (1998) 1 oz of peanuts contains: 160 kcal; 1.9 g saturated fat; 6.0 g monounsaturated fat; and 4.4 g polyunsaturated fat.

One oz (2 tablespoons) of peanut butter contains about the same.

The recommended 1.5 oz of peanuts daily contains 240 kcal, about 12% of a 2000 kcal diet. If added to the regular diet, this would lead to considerable weight gain over one year.

4 -7 CALORIC SWEETENER CONSUMPTION AND DYSLIPIDEMIA AMONG US ADULTS

See under SWEETENERS

FEEDING TUBES

“A Disconnect With the Existing Evidence Of Their Effectiveness.”

2-5 HOSPITAL CHARACTERISTICS ASSOCIATED WITH FEEDING TUBE PLACEMENT IN NURSING HOME RESIDENTS WITH ADVANCED COGNITIVE IMPAIRMENT

The decision to place a feeding tube (FT) in a patient with advanced dementia is one of the sentinel decisions that family members and health care professionals grapple with, in the nursing home (NH) environment.

Many patients with advanced cognitive impairment have a FT inserted during an acute-care hospitalization (usually for an infection).

Two widely cited literature reviews conclude that use of FT does not improve survival, prevent aspiration pneumonia, prevent decubitus ulcers, or improve other clinical outcomes.

The objective of this study was to show the variation and to identify the characteristics of acute care hospitals associated with rates of FT insertion. It included over 163 000 NH patients with advanced cognitive impairment admitted to a hospital between 2000 and 2007. None had FT in place on admission; all were over age 65 and severely functionally impaired. A total of 19 847 FT insertions occurred in the hospital (94% by percutaneous gastrostomy).

The rate of FT insertions varied between 0 and 40 per 100 admissions (mean per 100 admissions = 8).

A higher rate of FT insertions was independently associated with for-profit hospitals vs hospitals owned by state or local governments (absolute difference = 3 insertions per 100 admissions); hospitals with a greater number of beds and ICU use; and among blacks, a 2-fold increase compared with whites.

“Feeding tube insertion in persons with advanced cognitive impairment demonstrates a disconnect with the existing evidence of their effectiveness.”

Written advanced directions, do not resuscitate orders, and orders to forego artificial hydration and nutrition were associated with *lower* use of FT. But, prevalence of advanced directions in nursing home residents is low. Improving advanced care planning is essential to ensure that FT insertion is based on informed patient preferences.

Conclusion: Among nursing home residents with advanced cognitive impairment, those admitted to larger hospitals, and hospitals with for-profit ownership and greater ICU use were associated with increased rates of FT insertion.

The article stated that the rate of FT placement declined over the years. We may be making progress. The decision about care (including FT insertion) of severely demented patients should be made long before any hospitalization occurs.

Do you wish your demented loved-one to be admitted to the hospital for any reason? If there were no admission, some problems would be solved.

HEALTH BEHAVIORS

Combined, Four Adverse Behaviors Decreased Life Expectancy By About 12 Years.

4-1 INFLUENCE OF INDIVIDUAL AND COMBINED HEALTH BEHAVIORS ON TOTAL AND ALL-CAUSE MORTALITY IN MEN AND WOMEN

Specific health behaviors, cigarette smoking, physical inactivity, higher alcohol intake, and diets low in fruits and vegetables are associated with increased risk of cardiovascular disease, cancer, and premature mortality. All are modifiable. They frequently coexist.

This study examined the individual and collective influence of the 4 poor health behaviors on 20-year risk of total and cause-specific mortality in men and women from a UK-wide population-base. (n = 4886)

The target was the entire adult population of England, Wales, and Scotland who were 18 years or older in 1984-85. Selected one person from randomly selected addresses.

A questionnaire asked about frequency of 4 adverse health behaviors:

Alcohol consumption: over 21 units a week for men; 14 for women. (Unit = 8 g)

Smoking: current cigarette smoker (Past and never-smokers were excluded)

Physical activity (**PA**): spending little or no leisure time in PA (< 120 minutes a week)

Fruit and vegetable consumption: less than 3 times a day on a yearly basis

Baseline characteristics (1984-85) and follow-up (20 year) hazard ratios (**HR**) for mortality:

	All subjects (%)	Deaths (n/n)	HR (total mortality)	
				Reference
Age (mean)	44	1080/4886		
Current smoker (%)	44	497/2123	1.83	(vs never or prior smoker)
Alcohol intake (> 21)	17	178/836	1.33	(vs 0 intake)
PA min/ wk (% < 120)	64	937.3147	1.51	(vs > 540 min/wk)
Fruit and veg. (times / day)				
1	9	105/421	1.31	(vs 5 or more. / d)
2	26	287/1280	1.10	
3	32	358/1550	1.12	

(Each adverse behavior increased mortality)

Poor health behaviors (0 to 4) in relation to 20-year mortality

(% of subjects) HR for all cause mortality:

0 (8%)	1.00 (reference)
1 (26%)	1.85
2 (37%)	2.23
3 (23%)	2.76
4 (6%)	3.49

Combined, four adverse behaviors decreased life expectancy by about 12 years.

The combined effect of 4 poor health behaviors was associated with significantly higher mortality from cancer, CVD, and all other causes.

Individuals who exhibited all 4 poor health behaviors had, over 20 years, about 3 times the risk of death from CVD, and cancer, and 4 times the risk of dying of other deaths compared with those exhibiting no poor health behaviors.

Conclusion: In the contemporary population of the UK, cigarette smoking, high consumption of alcohol, low consumption of fruits and vegetables, and low levels of physical activity were associated, both independently, and when combined, with increased risk of premature death. Modest, but sustained, improvements in diet and lifestyle could have significant public health benefits.

Practical pointers has abstracted similar articles in the past. This reminder is helpful.

Note that fewer than 10% of the UK population in 1985 observed all 4 healthy lifestyles. I doubt observance was better in the US in 1985. Compliance is likely somewhat better now,

HUMAN GENOME

At Present, “Genomics Are More Closely Aligned With Modern Science than With Modern Medicine”

5-7 TEN YEARS ON--THE HUMAN GENOME AND MEDICINE

(This editorial was written by Harold Varmus, former director of the NIH and Nobel prize winner for discovery of retroviral oncogenes.)

Now, after the first decade of a postgenomic world, only a handful of major changes have entered routine medical practice: some gene-specific treatments of a few cancers; some novel therapies for a few mendelian traits; and some strong genetic markers for assessing drug responsiveness, risk of disease, or risk of disease progression. Most of these can be traced to discoveries that preceded the unveiling of the human genome.

Implicated haplotypes collectively account for only a small fraction of the apparent heritable risk. More than one decade of genomics will be required to understand the inborn risks of most common disorders, such as diabetes and hypertension.

Despite remarkably rapid advances, genomics are more closely aligned with modern science than with modern medicine. Only a few selected items of that new information are widely used as guides to risk, diagnosis, or therapy.

Changes in the worlds of commerce, law, regulation, ethics, health insurance, and information technology are intersecting with the expanded role of genetics in medicine.

The practice of direct-to-consumer marketing, mainly identification of SNPs as putative markers of disease risk, has been among the most visible manifestations of genomics. Yet this practice is not regulated, lacks external standards for accuracy, has not demonstrated economic viability, or clinical benefit, and has the potential to mislead customers.

Individuals who consent to genomic screening lack informed consent. They consent to the test, but the consent is not informed. They may be grievously misled. Informing patients that they have an increased risk of a certain disease does not inform how large the risk is, or whether a patient will ever develop the disease. For most screening tests, there is uncertainty about validity and clinical utility.

The likelihood of false positive tests is high. The test may be positive and “statistically significant” but clinically meaningless. The positive predictive value is very low. Patients may be informed that their risk is twice as great as average. This may mean risk is increased from 1% to 2%.

A positive screening test will cause increased anxiety, and lead to multiple follow-up tests further increasing concern, worry, and expense without any benefit.

In my view, offering and applying a screening test, not knowing and not being able to fully inform the patient about possible harms, is unethical.

Genomic screening has no place in primary care medicine. However, we may enjoy following developments while we learn more about it, while we try to improve the application of the valid screens we already have: family history, lifestyle factors, and established clinical and laboratory tests.

Screening should be sharply focused, and suggested, and supervised by an expert. It may have a place in high-risk families.

It will take decades of experience to settle on the clinical meaning of some genomic tests. We are still debating the effectiveness of breast and prostate cancer screening.

Ask: will the patient be better off knowing this information?

HYPERTENSION

“The Case Remains Open”

1-8 ANTIHYPERTENSIVE AGENTS AND PREVENTION OF DEMENTIA

Various studies have shown an association between mid-life hypertension (especially if untreated) and likelihood of developing dementia. This raises the possibility that antihypertension drugs might offer a form of prevention.

A prospective cohort study in this issue of BMJ reported the possible role of angiotensin receptor blocking (ARB) agents in reducing risk of dementia and in slowing its progression. The study followed over 800 000 male subjects older than age 65 with cardiovascular disease. and found significantly lower hazard ratios for incident dementia associated with ARBs than with the ACE inhibitor lisinopril (HR = 0.81) and with other cardiovascular drugs (HR = 0.76).

In patients with preexisting AD, ARBs were associated with a lower risk of admission to a nursing home.

Association does not prove causation.

Effects of combined ACE-inhibitors and ARB may be additive.

The public health implications of finding an effective way for preventing dementia are immense.

Further work is needed to verify the usefulness of antihypertensives in general and ARBs in particular

I abstracted this article as a provocative intervention to be aware of.

I will look for follow-ups.

We would expect some reduction in vascular dementia by control of BP.

“Dietary Management Is Appropriate For All Patients with Hypertension”

6-3 DIETARY THERAPY IN HYPERTENSION

THE CLINICAL PROBLEM

“Morbidity increases among persons whose blood pressure is above 115/75.”

The prevalence of hypertension increases dramatically with age, from about 10% in persons age 30, to 50% in age 60. However, some persons, including strict vegetarians, and those whose sodium intake is low, have virtually no increases in hypertension with age.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

The 3 corners of dietary treatment--a healthful diet, reduced sodium intake, and reduced body fat--influence the pathophysiology at many points of hypertension control.

High sodium intake is strongly correlated with the development of hypertension. It leads to increased intravascular fluid volume, cardiac output, peripheral resistance and higher BP.

Other factors contribute to pathophysiology of hypertension:

Stiffening of large conduit arteries in the elderly.

Vasoconstriction due to endothelial dysfunction and proliferation of smooth-muscle cells in small vessels.

Increased activity of the sympathetic nervous system.

Both aging and obesity contribute.

Reduction in salt intake and weight loss are effective in lowering BP.

Decreases in abdominal visceral fat improves function of both conduit and resistance vessels.

CLINICAL EVIDENCE

The Dietary Approaches to Stop Hypertension (DASH) was especially effective in patients who had hypertension. When combined with low salt intake, benefit was greater. When weight loss was added to the diet, BP was reduced to a greater extent.

Sodium reduction, the DASH diet (vs controls), and changes in systolic BP:

Sodium	Controls	DASH
3.5 g daily	143 mm Hg	135 mm Hg
2.3 g	141	133
1.2 g	135	128

(Note the systolic BP of the controls was also lowered by salt restriction.)

CLINICAL USE

Dietary management is appropriate for all patients with hypertension, and for those with pre-hypertension. In simple terms:

Eat poultry, fish, nuts, legumes, low-fat and non-fat dairy, vegetables, fruit, whole grains poly-unsaturated and mono-unsaturated fats (olive, canola, soybean, peanut, corn, sunflower, safflower oil)

Avoid red meat, full fat dairy, snacks and desserts high in sugars, white flour, butter, coconut oil, palm-kernel oil, sweetened beverages, candies, and cookies. Canned and processed foods should be limited unless their salt content has been eliminated

GUIDELINES

1.5 g sodium per day (~ 4 g salt) is optimal. A BMI less than 25 is also recommended. Alcohol intake is limited.

“A trial of intensive dietary treatment is warranted for 6 months to try to achieve the target goal for blood pressure (systolic < 140 and diastolic < 90) before medication is introduced.”

Patients should monitor their BP at home.

These dietary recommendations are almost identical (except for stricter sodium content) to diets recommended for atherosclerotic disease. However, I believe few (if any) patients with hypertension treated in primary care would continue a greatly reduced sodium and calorie diet. Some strict vegetarians will have less of a problem.

Why? Humans naturally crave sweets and salt. Our children are reared using sweets as a “treat” and “reward”. They contain high levels of sodium and sugar. Craving is both in-born and fostered by our society. The same difficulty exists for diets to control weight.

However, even a modest reduction in salt may benefit.

The article did not mention the helpful role of potassium in BP control. As sodium content of the diet decreases, potassium increases to add to therapeutic benefit.

A greatly reduced sodium diet may be harmful in some (especially older) patients who are being treated with diuretics and become dehydrated.

The authors recommend dietary treatment for 6 months before drug therapy is started. I doubt many primary care clinicians will follow this advice. Diet is unlikely to be followed, and unlikely to succeed in reducing BP. Primary care physicians will avoid temporizing with drug treatment.

INFLUENZA

Oseltamivir Ring Chemoprophylaxis Was Effective In Reducing an Outbreak of 2009 H1N1 Flu

6-6 OSELTAMIVIR RING PROPHYLAXIS FOR CONTAINMENT OF 2009 H1N1 INFLUENZA OUTBREAKS.

This study describes the Singapore experience in responding to 4 outbreaks of 2009 pandemic influenza A (H1N1) virus in military camps and evaluates the role of oseltamivir “ring chemoprophylaxis” in attenuating transmission of the virus.

A suspected case of influenza was defined as influenza-like illness (temperature 38° or more, with cough or sore throat) with onset of symptoms within 7 days after travel to an affected area, close contact with a person with confirmed infection, or contact with a local cluster of infected persons.

Prompt laboratory confirmation was by polymerase-chain-reaction.

Contacts were defined as persons who had unprotected exposure to an infected person since the day before to onset of symptoms. Most contacts were quarantined at home for 7 days.

A 10-day course of *Tamiflu* was administered to coworkers for 10 days after exposure to an infected person. (Coworker defined as a member of the same military unit where contact opportunities were substantial. Larger prophylaxis rings were instituted if cases were present in multiple units.

Summary of 4 outbreaks:

Total number of personnel	1175
Confirmed cases	82 (7%)
Before intervention	75 (6.4%)
After intervention	7 (0.6%)

(After prophylaxis began, in combination with home leave to avoid contacts, only 7 more cases were confirmed.)

All 7 cases with onset after prophylaxis occurred within 4 days after the intervention.

Adverse effects of oseltamivir: 8% reported mild, non-respiratory symptoms. There were no neuropsychiatric events; no severe adverse events reported.

“In the present study, we have shown that ring prophylaxis with oseltamivir, given after exposure in military camps was effective, allowing training and operations to continue while substantially reducing the risk of further generations of cases during prophylaxis.”

Ring prophylaxis based on spatial proximity was more effective in controlling the spread of disease than was the focus on close contacts.

Early case detection and use of antiviral ring prophylaxis effectively truncated the spread of infection during an epidemic. Aggressive prophylaxis may be justifiable to protect vulnerable populations such as frail or elderly residents of long-term care facilities, or persons in closed communities.

Conclusion: Oseltamivir ring chemoprophylaxis, together with prompt identification and isolation of infected personnel, was effective in reducing the impact of the outbreak of 2009 H1N1 influenza in semi-closed settings.

Application of ring prophylaxis and quarantine would, of course, be much more difficult in primary care practice than in the military.

I believe ring prophylaxis is a valuable intervention to contain epidemics. It may be especially effective in controlling flu in hospitals, nursing homes, retirement communities, and in air travelers.

In households of a case of flu, prophylaxis of the entire family may prevent infection and allow members who must work outside the home to protect their contacts.

Ring prophylaxis does not act alone. Isolation and quarantine are essential. Vaccination is essential. Prophylaxis may be of value in years when the vaccine is a poor match for the circulating virus.

KIDNEY FUNCTION

“Prognosis Associated With A Given Level Of eGFR Varies Substantially Based On The Presence And Severity Of Proteinuria.”

2-3 RELATION BETWEEN KIDNEY FUNCTION, PROTEINURIA, AND ADVERSE OUTCOMES

This study determined the association between reduced estimated glomerular filtration rate (**eGFR**), proteinuria, and adverse clinical outcomes. The researchers postulated that patients with both reduced eGFR and proteinuria would be at higher risk of adverse outcomes.

Community-based outpatient cohort identified patients (n = over 920 00) with laboratory reports of both proteinuria and eGFR between 2002-2007. All had at least one outpatient measurement. None required renal replacement at baseline.

Estimated the GFR for each patient using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation.

Categorized GFR as mL/min /1.73m²: 1) 60 or greater, 2) 45-59.9, 3) 30 to 44.9, 4) 15 to 29.9

Protein was determined by random dipstick measurements: 1) normal (negative), 2) mild (trace or 1+), 3) heavy (2+ or greater).

Followed for a mean of 35 months. Main outcomes: all-cause mortality, myocardial infarction, and progression to kidney failure.

Three % died over the study period; 0.6% hospitalized for myocardial infarction; 0.08% initiated renal replacement therapy. 0.04% experienced a doubling of serum creatinine. The adjusted rates of these outcomes were all increased at lower levels of eGFR and at heavier proteinuria.

Adjusted likelihood of clinical outcomes by level of eGFR and proteinuria.

All cause mortality per 1000 person-years:

Proteinuria	Normal	Mild	Heavy
eGFR 60 or greater	2.7	5.8	7.2
45-59	2.9	5.2	7.2
30-44	4.0	5.8	7.5
15-29	6.7	9.1	10.4

(Within each stratum of eGFR, there was substantial variability in risk. Participants who had heavier proteinuria had markedly increased rates of all-cause mortality.)

Similar relative increases were evident in myocardial infarction and end-stage renal disease.

The adjusted mortality risk was more than 2-fold higher among individuals with heavy proteinuria and a eGFR of 60 or greater as compared with those with eGFR of 45-59.9 and normal protein excretion.

“We demonstrated that prognosis associated with a given level of eGFR varies substantially based on the presence and severity of proteinuria.”

Heavy proteinuria without overtly abnormal eGFR appeared to have worse outcomes than those with moderately reduced eGFR but without proteinuria.

These findings suggest that risk stratification performed in terms of eGFR alone is relatively insensitive to clinically relevant gradients in risk.

Conclusion: The risks of death, myocardial infarction and progression to kidney failure at a given level of eGFR were independently increased in individuals with higher levels of proteinuria.

I enjoy abstracting advances in primary care medicine that provide prognostic and therapeutic benefits at little cost. And that may actually reduce costs. Among these are: low-dose aspirin, the prognostic value of proteinuria, vitamin D (hopefully; maybe), and the Ottawa ankle rule.

METABOLIC SYNDROME

“All Begins With Excess Central Obesity”

1-6 THE METABOLIC SYNDROME

The metabolic syndrome (**MS**) has existed in various forms for more than 8 decades. Only in the past 5 years has real controversy about its definition and significance emerged.

The main controversy is that the syndrome has too many definitions, and there is a lack of clarity about its role and value in clinical practice.

The controversy drove the need for a single global definition.

Several prestigious organizations have combined to develop one unified definition, which has now been published.

The main difference between the NCEP ATP III and the new definition is the threshold value for waist circumference. Because the relation between waist circumference and cardiovascular disease and diabetes risk differs globally, national and regional cutpoints of waist circumference can be used.

Insulin resistance continues to explain most, if not all, of the MS. No other mechanisms have emerged that come close.

“Evidence now indicates that the metabolic syndrome all begins with excess central obesity”

When beta-cell function is responsive, hyperinsulinemia results and fasting and postprandial glucose often remains normal for years. In those genetically predisposed, defects in insulin secretion, and impaired fasting glucose and impaired glucose tolerance follow.

At present, however, drug therapy for the MS largely requires separate agents for treatment of dyslipidemia, dysglycemia, and hypertension.

“The metabolic syndrome is a widely accepted concept that identifies the centrally obese patient with increased risk for cardiovascular disease and diabetes.”

Lifestyle interventions remain the primary therapy. Drugs are used for residual risks for cardiovascular disease.

The metabolic syndrome now defined:

1. *Increased waist circumference Population-specific and country specific^a*
2. *Increased triglycerides 150 mg/dL and higher^b*
3. *Reduced HDL-cholesterol Males under 40 mg/dL; females under 50^b*
4. *Increased BP Greater or equal to 130/80^b*
5. *Increased fasting glucose Greater than 100 mg/dL*

a For many patients in the US, < 102 cm (40”) for males; < 88 cm (35”) for females

b History of use of drugs to lower levels is an alternative

Any combination of 3 will make the diagnosis.

A simple “eyeball test” can easily recognize patients with abdominal obesity and likelihood of the MS.

Extra-abdominal fat (out side the muscular abdominal wall) is not metabolically active. Intra-abdominal fat is the culprit, due to its drainage into the liver. This leads to other manifestations of the MS.

The MetS Does Not Provide Better Disease Prediction Than Its Individual Components. Unhealthy Lifestyles Are the Root Cause

3-2 THE METABOLIC SYNDROME AS A CLUSTER OF RISK FACTORS [Editorial]

Is the Whole Greater Than the Sum of Its Parts?

The MetS is a combination of 5 components.

Greater waist circumference

Hypertriglyceridemia

Hyperglycemia

Hypertension

Low HDL-cholesterol

(Any combination of 3 defines the syndrome):

Cardiovascular disease risks associated with the MetS are unstable and substantially heterogeneous, depending on which of the 5 components is included.

Each of the components of the MetS is already part of routine clinical assessment. Because treatment strategies are available for the individual risk factors rather than for the MetS itself, it is not clear whether the diagnosis of the MetS can improve treatment strategies.

A study in this issue of *Archives* conducted a pooled analysis from 7 clinical trials using intravascular ultrasound to compare the effects of MetS and its individual components on coronary plaque progression.

Results indicate that MetS does *not* predict coronary plaque progression beyond the independent risk contributions of its individual components. It does not represent a distinct disease syndrome.

Obesity, especially abdominal adiposity, is a driving force for other components of MetS. Many obese individuals possess some, but may not possess all components. Non-obese individuals can also possess several components.

Central obesity is at least one factor commonly shared by all other components, with waist circumference serving as a point of further clinical emphasis. MetS has increased attention to central adiposity.

Because all 5 components are modifiable by changes in diet and physical activity, the recognition of MetS is highly relevant for prevention. Identifying “fellow travelers” of MetS such as sleep apnea, fatty liver, gout, gallstones, and polycystic ovary syndrome will help identify high-risk patients.

Unhealthy lifestyles are the root cause of all components of MetS.

In this group of patients with established CHD, 58% had the MetS. I would have thought that almost 100% would have the syndrome.

Since we do not have a “pill” for the MetS, we rely on treatment of all components in individual patients. As each component, added to others, increases risk, treating each component will decrease risk. Will informing a patient that he has 4 or 5 combined risk factors for CAD impress him enough to change lifestyle? It may impress some individuals.

Insulin resistance is the basic metabolic defect related to the syndrome. This, I believe, is largely due to intra-abdominal obesity.

I call the MetS the “Mall syndrome”. Observing people in a busy shopping mall will reveal how many Americans have increased abdominal girth.

MYOCARDIAL INFARCTION

3-7 REMOTE ISCHAEMIC CONDITIONING BEFORE HOSPITAL ADMISSION AS A COMPLEMENT TO ANGIOPLASTY, AND EFFECT ON MYOCARDIAL SALVAGE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION See under REMOTE ISCHAEMIC CONDITIONING

NONALCOHOLIC STEATOHEPATITIS

Both Are Associated With Improvement Over 2 Years

5-6 PIOGLITAZONE, VITAMIN E, OR PLACEBO FOR NONALCOHOLIC STEATOHEPATITIS

Nonalcoholic steatohepatitis (**NASH**) is a common liver disease characterized histologically by hepatic steatosis, lobular inflammation, and hepatocellular ballooning. It progresses to cirrhosis in up to 15% of patients. It is closely associated with features of the metabolic syndrome: insulin resistance, obesity, hypertriglyceridemia, and type-2 diabetes.

This phase 3 study investigated whether either pioglitazone (to ameliorate insulin resistance) and vitamin E (to ameliorate oxidative stress) would improve NASH.

Multicenter, randomized, placebo-controlled, double-blind clinical trial assigned 247 adults with NASH to : 1) pioglitazone (*Actos*; Takeda) 30 mg daily, or 2) vitamin E 800 IU daily), or 3) placebo. No patient had diabetes. No subject consumed alcohol more than 20 g per day for women, and 30 g per day for men. None had other liver diseases or heart failure. All subjects were given a standardized set of pragmatic recommendations about lifestyle and diet.

Primary outcome = improvement in histological features of NASH assessed by use of a composite of standardized scores for steatohepatitis: lobular inflammation; hepatocellular ballooning; and fibrosis.

Outcomes over 96 wk	Improvement (%)	NNT to benefit one subject
E vs placebo	43 vs 19	4
Pioglitazone vs placebo	34 vs 19	7 (Not statistically significant)

These data cannot be generalized to patients with diabetes, or those with cirrhosis.

Given that relapse occurred after discontinuation of the drugs, it is likely that they will have to be taken indefinitely. The weight gain with pioglitazone did not resolve after discontinuation. This also detracts from its long-term usefulness.

The unknown potential for adverse effects of the drugs must be factored into the decision about whether to use these drugs.

Conclusion: Vitamin E was superior to pioglitazone for treatment of NASH in adults without diabetes. Significant benefits of pioglitazone were observed in some of the secondary outcomes.

I found this article difficult to abstract. I debated whether to include it. The full primary outcome is convoluted. (See the full abstract.) Although this drug therapy is not suited for primary care at this time, I believe we should keep it in mind.

NASH is a common and serious disease. Diagnosis is usually made by CT scan of the liver.

The study strongly suggests that both drugs are effective in treatment of NASH. But, the long-term adverse effects and effectiveness of pioglitazone and vitamin E used in this manner are not known. Look for further developments.

Weight loss remains the effective therapy. I included the article in part to point out the intransigence of overweight and obese patients. They know that they are at increased risk of disease and death, and NASH increases risk. Obesity is an unsolved problem.

NUTS

5-3 NUT CONSUMPTION AND BLOOD LIPID LEVELS See under DYSLIPIDEMIA

OBESITY

Requires Continuing 60 Minutes of Moderate Physical Activity Every Day if Diet Maintained .

4-2 PHYSICAL ACTIVITY AND WEIGHT GAIN PREVENTION

This study examined weight changes associated with different physical activities (PAs) in a large cohort of women followed for up to 13 years (between ages 54 to 67).

Prospective cohort study involved 34 079 healthy women (mean age 54 at baseline) from 1992 to 2007. Women reported their PA and body weight at baseline and months 36, 72, 96, 120, 144 and 156.

Estimated the energy expended in metabolic equivalents (MET hours) per week.

Classified as expending: 1) less than 7.5 MET hours per week; 2) 7.5 to 20.9; 3) 21 and over per week. This was equivalent to: 1) 150 minutes moderate PA weekly (as recommended by the federal government); 3) over 420 minutes moderate PA per week (~ 60 minutes per day as recommended by the Institute of Medicine).

Women continued to consume their regular diet.

Main outcome = change in weight over 13 years

Defined normal weight as BMI < 25.

Baseline (1992) characteristics Physical activity level (MET hours / week)

	< 7.5	7.5-20.9	21 and over
% of women	50	29	22
BMI	27	26	25

In this large cohort of middle-aged and older women who continued their usual diet for up to 13 years, there was an overall weight gain..

Only in a subset of women, whose BMI was under 25 at baseline, and who engaged in moderate PA for an average of 60 minutes daily over the years, was BMI maintained below 25. This is the level recommended by the IOM.

Compared with women who engaged in the equivalent of 420 minutes per week (~ 60 minutes per day) of moderate PA, those carrying out 150 to less than 420 minutes per week, as well as those engaged in less than 150 minutes per week, gained significantly more weight. There was no difference in weight gain between the 2 lesser active groups.

. These results highlight 2 important points:

- 1) Once overweight, it may be too late to prevent weight gain by exercise alone over the years.
- 2) Sustaining high levels of PA in middle age (60 min /day) is needed to successfully maintain normal BMI, and to prevent weight gain. Women who engaged in this amount of PA at baseline, but did not sustain it, gained weight at a similar trajectory as less active women.

Preventing weight gain is preferable to treating overweight and obesity because of the limited sustainability of weight loss. Most persons who do manage to lose 10% of weight cannot sustain the loss at 24 months.

Because weight gain results from an imbalance between energy intake and energy expenditure, an important question for weight gain prevention among individuals consuming a usual US diet is the amount of PA needed. The 2008 federal recommendation for 150 minutes per week, while clearly sufficient to lower the risks of chronic diseases, is insufficient for prevention of weight gain absent calorie restriction.

Conclusion: In this large 13-year prospective study, women (while aging from 54 to 67) who 1) consumed their usual diet, 2) had a BMI under 25 at baseline, and 3) sustained moderate-intensity PA for an average of approximately 60 minutes per day, maintained their weight.

PA was inversely related to weight gain only among women with a BMI < 25 at baseline. Among women with a BMI over 25 at baseline, weight continued to increase. Controlling caloric intake in the latter group is important.

In general, as we age, PA incrementally decreases. If we do not incrementally decrease energy intake, we gain weight.

In this study, 13% of women did not reduce PA. They continued at about 60 minutes daily between ages 54 and 67 while maintaining their usual diet. This is an unusual achievement.

As noted, two factors are required to avoid weight gain. 1) Maintaining a BMI < 25 as age 55 is approached, 2) Continuing about 60 minutes of moderate PA daily over the following years.

Relatively few persons can do this. Most of us who maintain a low BMI must gradually decrease caloric intake as we age.

1-3 EXTRA CALORIES CAUSE WEIGHT GAIN--BUT HOW MUCH?

See under WEIGHT GAIN

OSTEOARTHRITIS

A Potentially Modifiable Risk Factor For Knee OA.

3-5 ASSOCIATION OF LEG-LENGTH WITH KNEE OSTEOARTHRITIS

Leg-length inequality (**LLI**) is common. It has been implicated in: low back pain, trochanteric bursitis, osteoarthritis (**OA**) of the hip and knee, knee pain, and Achilles rupture.

LLI increases ground-reaction forces on the lower leg. Because it has to come from a higher level to reach the ground during walking, a shorter leg would likely incur an increased ground-reaction force compared with the legs that are equal in length.

Like walking down hill

The study followed over 2900 participants age 50-79 (mean age 63); at high risk for OA due to knee pain, obesity (mean body mass index = 31), knee injury or surgery. Performed standard knee radiography and full-limb radiography to determine length.. Follow-up = 30 months.

Risk of incident symptomatic OA of the knee, and progressive OA increased in the shorter leg over 30 months

Leg-length inequality may be an important risk factor for knee OA, primarily in the shorter leg.

LLI may be under-recognized and under treated in patients with knee OA. It is easily corrected

with shoe modification. This raises the possibility that correction of LLI may be a simple and cost-effective method for preventing and treating and knee OA.

Conclusion: Radiographic LLI was associated with prevalent, incident symptomatic and progressive knee OA. LLI is a potentially modifiable risk factor for knee OA.

I wonder--Will the NIH now sponsor a long-term treatment trial?

This may be a simple application for primary care. Patients with obvious LLI are not uncommon.

Would it be reasonable to advise them to obtain a shoe lift?

Would it be reasonable to tape-measure the lower extremities in patients with established knee OA to determine if LLI is present, and if a lift would possibly benefit? This might be helpful especially in younger individuals to retard development of knee OA.

PERIODONTAL DISEASE

6-5 TOOTH BRUSHING, INFLAMMATION AND RISK OF CARDIOVASCULAR DISEASE

See under **CARDIOVASCULAR DISEASE**

PHYSICAL ACTIVITY

4-2 PHYSICAL ACTIVITY AND WEIGHT GAIN PREVENTION See under OBESITY

PNEUMONIA

Reduces Incidence Of Pneumonia And Death From Pneumonia. But Should We Recommend It?

3-8 EFFICACY OF A 23-VALENT PNEUMOCOCCAL VACCINE IN PREVENTING PNEUMONIA AND IMPROVING SURVIVAL IN NURSING HOME RESIDENTS

This trial determined the efficacy of a 23-valent vaccine in nursing homes (NH) in Japan.

At baseline, about 90% of subjects were over age 75; 47% age 85-94; 9% age 95-1005. About 10% were bedridden, 5% had a “psychological disorder”. The majority had 1 to 3 or more co-morbid conditions. Written informed consent was obtained from participants or their next of kin.

Excluded patients who were immunocompromised and those who were unable to follow instructions.

Incidence of pneumonia over 3 years:	Vaccine (n = 502)	Placebo (n =504)
Pneumococcal	14	37
Non-pneumococcal	49	67

All-cause pneumonia	63	104
Death rates		
Pneumococcal pneumonia	0/14	13/37
Non-pneumococcal pneumonia	13/49	13/67
All cause pneumonia	13/63	26/104

The death rates from all-cause pneumonia and non-pneumococcal pneumonia and the incidence of non-pneumococcal pneumonia were not significantly reduced in the vaccine group.

Overall, death rates did not differ between groups; (80 patients in each group died from all causes).

“The findings of this study suggest the need for a national policy that recommends the systematic vaccination of residents living in institutions to reduce morbidity as well as the cost of health care in Japan.”

Conclusion: The 23-valent pneumococcal vaccine prevented pneumococcal pneumonia and reduced mortality from pneumococcal pneumonia in nursing home residents.

I did not abstract this study because of its conclusions, but to ask: Should we give pneumococcal vaccine to NH patients? If so, to whom? If not, to whom?

The investigators noted that: “A placebo controlled trial of vaccine efficacy has been deemed unethical in developed nations where the vaccine is considered standard of care, even in the absence of any proved efficacy.” In Japan there is no national recommendation for its use. Does the “standard of care” of NH residents in the USA include pneumococcus vaccine?

The trial did place some restriction on participants. Only 5% had a “psychological disorder”. Although participants were very old and had co-morbidities, only 160 of the 1006 residents died over 3 years. Terminal cancer patients must have been excluded.

The prevalence of dementia in NH in the USA, I believe, is much higher than 5%. The study excluded those who were unable to follow directions. The investigators did obtain informed consent from the patient or surrogate.

If vaccination were universal in NH in the USA, all patients would have to give informed consent. Many would lack decisional capacity to give informed consent. This would involve finding, fully informing, and obtaining consent from surrogates.

I believe the kindest and most appropriate approach would be to be very restrictive in asking individual patients if they wish to receive vaccine. Many patients in NH do not wish to extend a demented life. (At any rate, vaccination did not reduce the death rate.) Should we bring up the subject up very often? I believe not.

Remember Osler's comment: "Pneumonia is the old man's friend"

As usual, the decision rests on the individual patient's informed consent. I would ask only those who have a reasonable remaining length of enjoyable life.

QRISK2 RISK SCORE

6-1 AN INDEPENDENT AND EXTERNAL VALIDATION OF QRISK2 CARDIOVASCULAR DISEASE RISK SCORE See under CARDIOVASCULAR DISEASE

REMOTE ISCHAEMIC CONDITIONING

"Increases Myocardial Salvage, And Has A Favorable Safety Profile."

3-7 REMOTE ISCHAEMIC CONDITIONING BEFORE HOSPITAL ADMISSION AS A COMPLEMENT TO ANGIOPLASTY, AND EFFECT ON MYOCARDIAL SALVAGE IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

Remote ischemic conditioning (**RIP**) is a simple procedure: 1) applying a BP cuff to the arm and inflating to 200 mm Hg and continuing inflation for 5 minutes. 2) Deflating the cuff and leaving it deflated for 5 minutes. 3) repeating the cycle a total of 4 times (total of 40 minutes if the final deflation period of 5 minutes is included). The procedure can be applied immediately after symptoms of a suspected MI occur. It may be given by ambulance or other personnel at the scene and continued during transport.

This study used myocardial imaging with repeated ⁹⁹technetium scans to examine whether RIP done before percutaneous coronary intervention (**PCI**) increases myocardial salvage in patients with an evolving first MI.

The primary outcome was myocardial salvage index at 30 days after PCI measured by myocardial perfusion imaging as the proportion of the area at risk salvaged by treatment. Salvage index was calculated as (area at risk - final infarct size) / area at risk.

251 subjects with acute ST elevation MI were randomized telemedically to: 1) RIP, and 2) no RIP. Patients received RIP during transport to the hospital, started by ambulance personnel.

Mean salvage index was 0.69 treated vs 0.57 controls, a difference of 0.12.

Salvage as a percentage of left ventricle was (statistically) significantly higher in the RIP group (16% vs 11%). Differences in final infarct size were not significant (median 7% of left ventricle in both groups).

Peak troponin T release, the proportion of patients achieving 70% ST segment resolution within 90 minutes, and NYHA class of disease at 30 days did not differ between groups.

Major adverse coronary events were similar in each group: 3 deaths; 1 reinfarction; 3 heart failure.

Conclusion: “Remote ischemic conditioning before hospital admission increases myocardial salvage, and has a favorable safety profile.”

Ordinarily, I would not include this study. It is not a practical point at this time. Will it ever be? I included it because it is so provocative. I will be on the lookout for further developments.

How does RIP influence the coronary circulation? The authors did not discuss this. There are no studies about the effect of RIP on the coronary circulation (Personal communication from Dr. Botker) They seem, however, enthusiastic about the benefits of the procedure. I remain skeptical. The procedure resulted in no clinical benefits.

RICE

[5-2] WHITE RICE, BROWN RICE, AND RISK OF TYPE-2 DIABETES IN US MEN AND WOMEN See under **DIABETES:**

RING PROPHYLAXIS

[6-6] OSELTAMIVIR RING PROPHYLAXIS FOR CONTAINMENT OF 2009 H1N1 INFLUENZA OUTBREAKS See under **INFLUENZA**

RISK PREDICTORS

Should Have A Favorable Risk-Benefit Ratio, Reasonable Cost, Acceptability, And Convenience.

4-6 WHAT MAKES A GOOD PREDICTOR? The Evidence Applied to Coronary Artery Score

Each year, researchers identify thousands of potential new “tools” for predicting patients’ medical futures. There is heightened interest for discovering, validating, and incorporating predictors into clinical practice. Very few predictors eventually change practice.

What makes a good predictor?

A good predictor is one that has a favorable risk-benefit ratio, reasonable cost, acceptability, and convenience. Proper evidence ideally requires randomized trials demonstrating that using the predictor improves decision-making and clinical outcomes without inordinate adverse events. It also requires cost-effectiveness analysis, integrating benefits, risks and costs.

However, hardly any predictors in the literature, or even those routinely adopted in clinical practice, have their effectiveness proven in randomized trials.

A comprehensive checklist for a predictor might be:

- 1) Predicts diseases with major morbidity
- 2) Effective treatment must be available
- 3) The treatment should *not* be equally effective (or equally risky) for all persons
- 4) Allows more accurate classification of individuals into categories in which treatment is or is not indicated
- 5) The incremental prediction should be accomplished beyond what can be achieved with information already available
- 6) There should be consensus about, and standardization of, established routine predictors
- 7) The predictor should be unambiguously defined and measured

Most published research on predictors is irrelevant or tangential to this check list. Almost all articles report statistically “significant” results. This means little. Many investigators deal with whether a predictor in isolation has any ability to predict something. This does not consider that many clinical facts and routine laboratory predictors may already inform prognosis. Thus, it is often not clear whether the new test adds incremental prognostic information.

The Framingham risk score is the most quoted in the current literature. It includes age, total cholesterol, HDL cholesterol, smoking, systolic BP, history of treated hypertension.

It estimates risk of a cardiovascular event over the next 10 years.

Score can range from a low risk <10%; intermediate risk 10% to < 20%; and 20% and over high risk

Low risk patients need not be treated with preventive therapy. High risk patients should be treated. Intermediate risk patients may or may not be treated.

I do not believe many primary care clinicians use the Framingham. It is possible for a 30-year old man who smokes to have a low score. Primary care physicians look far beyond 10 years. They include many other risk factors: family history, body mass index, abdominal obesity, peripheral atherosclerosis. We act on all those who are present, regardless of age of the patient. And on lifestyles in addition to smoking, physical activity, excess alcohol, and diet.

Primary care physicians deal with the general population. Specialists deal with a very select subgroup. They may be tempted to use, and be expected to use the “latest and the best” technology.

I believe we do not need any more risk factors for CVD. We have failed miserably to apply those we now have. The CACS does not add to risk- prediction for primary care patients.

Risk Scores Will Inevitably Become Outdated

6-1 AN INDEPENDENT AND EXTERNAL VALIDATION OF QRISK2 CARDIOVASCULAR DISEASE RISK SCORE

“General practitioners need an accurate and reliable tool to help them identify patients at high risk of having a cardiovascular event.” Many risk scores have been developed to estimate 10-year risk based on known risk factors.

After development of a score, it must be externally validated. This article describes results of the validation of a new risk score (**QRISK2**)

In the UK, until recently, NICE recommended use of the long-established Framingham equation. Subsequently, NICE developed an adjusted version of Framingham (**N-F**).

In this study, participants were patients registered in the UK database between 1993 and 2008. The cohort consisted of 1 583 106 patients among 365 general practices (median age 48; IQR 41-59). Median follow-up = 6.2 years.

Primary outcome = first diagnosis of cardiovascular disease (MI, angina, coronary heart disease, stroke, transient ischemic attack).

The incidence of CVD varied widely between different ethnic groups.

Risk classification used a 20% or greater risk of a CVD event over the next 10 years. (The cutpoint used in the UK to treat with statins.)

Calculated QRISK2 score (10-year estimated risk of CVD). Determined actual observed incidence of CVD. Calculated how many patients would be reclassified using QRISK2 compared with N-F:

Among men, predicted to be at high risk (>20%) of a CVD event, actual incidence of CVD per 1000 patient-years was 27.8 with QRISK2, and 21.9 with N-F. Among women, incidence was 24.3 and 21.9

A total of 11.6% would be reclassified:

1.8% classified as low risk (<20% by QRISK2) with N-F would be upgraded to high risk with QRISK2. 45% classified as high risk by N-F would be downgraded to low risk by QRISK2.

N-F grossly over-estimated risk

The actual observed risk of CVD in these patients was 14.00%. The mean predicted high-risk by QRISK2 was 14.98%, and the mean predicted high-risk by N-F was 25.14%

Risk scores will inevitably become outdated with improvements in clinical outcomes and data

recording, and changes in population demographics. QRISK2 will undergo annual upgrades.

Conclusion: QRISK2 is more accurate than N-F in predicting a high-risk population in the UK.

I congratulate the investigators on completion of this massive cohort study.

In the UK, the cutpoint of 20% risk of CVD over the next 10 years is used to determine drug treatment. Those with 20% or more risk should be treated with drugs (usually statins). Those between 10% and 20% are doubtful. Those under 10% should not be treated.

My main reason for abstracting this study was to ask--How valuable are risk scores such as these for primary care practice in the US? How often do primary care physicians in the US use risk calculators? Do risk scores have much effect on clinical decision-making? Do they improve clinical outcomes? I doubt clinicians in the US use them very often. They will be more likely to treat individual risks, including dyslipidemia at an early age. And treat all risks simultaneously.

Primary care looks far beyond 10 years. The atherosclerotic process begins at an early age.

It is possible for a younger patient who has a high cholesterol to have a low score. And an obese, hypertensive patient to have a score under 20%.

Older patients often have high scores determined mainly by age.

The Framingham score has had a remarkable durability. After decades, it is still frequently quoted. I believe it is now outdated.

Risk scores may be useful in encouraging patients to adopt a more healthful lifestyle, and to be more compliant with treatment. Patients with high scores might be more likely to improve lifestyles and be more compliant with taking their medications.

SCREENING

Significantly Reduced Incidence and Mortality from CRC

5-4 ONCE-ONLY FLEXIBLE SIGMOIDOSCOPY SCREENING IN PREVENTION OF COLORECTAL CANCER

Screening can potentially prevent CRC because most arise from adenomas, predominantly symptomless growths that develop in 20-30% of the population.

Two thirds of CRCs and adenomas are located in the rectum and sigmoid.

Flexible sigmoidoscopy (FS) is well accepted, safe, and quick. It may be a suitable method for population screening.

This randomized trial examined the hypothesis that only one FS screen between ages 55-64 is cost effective, acceptable, and reduces CRC incidence and mortality. This is based on observations

suggesting that most people who develop a distal colon cancer will have developed an adenoma by age 60, and removal of adenomas by sigmoidoscopy offers protection against distal CRC.

The trial entered (1994-1999) 170 432 men and women, age 55-64 (mean age 60) from multiple centers in the UK. Those with a family history of CRC or symptoms of CRC were managed outside the trial because randomization would not have been in their interest.

Randomized (ratio of 1:2) to: 1) intervention group (offered a flexible sigmoidoscopy), or 2) controls (not contacted).

All adenomas were removed.

Those with adenomas larger than 10 cm, 3 or more adenomas, tubulovillous or severe dysplasia, or malignant disease were referred for colonoscopy.

Of the subjects actually screened, 95% were discharged because there were no polyps, or only low-risk polyps. 5% were referred for colonoscopy.

CRC incidence and mortality over a mean of 11 years:

A. Controls (n = 112 939)

Incidence of CRC	Cases	Rate per 100 000 person-years
Rectum and sigmoid	1192	98
Proximal	628	51
CRC mortality	538	44

B. Screened (n = 40 621)

Incidence of CRC	Cases	Rate per 100 000 person-years
Rectum and sigmoid	215	48
Proximal	224	50
CRC mortality	111	25

C. Hazard ratios (Screened vs controls)

Rectum and sigmoid	0.50
Proximal	0.97
CRC mortality	0.57

The estimated number of people needed to be screened to prevent one death due to CRC = 489.

There was a 43% reduction in death due to colorectal cancer in people who attended screening compared with controls.

There was no effect of screening on incidence of CRC in the proximal colon.

Economic analysis suggests that screening is cost-effective due to lower costs of treatment of CRC. Adequately trained nurses can undertake flexible sigmoidoscopy as competently as can

Gastroenterologists. Public acceptance of nurse-led sigmoidoscopy screening is high.

Conclusion: Flexible sigmoidoscopy is a safe and practical test, and when offered only once to people between ages 55-64, confers a substantial and long-lasting protection from CRC.

Relatively few persons in the US undergo colonoscopy.

I believe FS is not a substitute for colonoscopy. It is an added screening procedure.

Since sigmoidoscopy requires less elaborate preparation, is more convenient, can be performed by health-care personnel other than gastroenterologists, many more patients may be willing to accept it.

Screening sigmoidoscopy may be repeated periodically and augmented with fecal occult blood testing. Costs to patients and to society will be much lower.

Many CRCs were discovered during the one and only screening sigmoidoscopy and were successfully treated.

SIGMOIDOSCOPY

[5-4] ONCE-ONLY FLEXIBLE SIGMOIDOSCOPY SCREENING IN PREVENTION OF COLORECTAL CANCER See under COLORECTAL CANCER

STATIN DRUGS

Quantifying The Risks And Benefits Of Statins At The Population Level.

6-2 UNINTENDED EFFECTS OF STATINS IN MEN AND WOMEN IN ENGLAND AND WALES

This large population-based study examined a range of clinical outcomes that are positively and negatively associated with statin use.

A prospective study, derived from a computer-based medical information system (2002-2008) in the UK, included patients (age 30-84).

Identified new users of statins during the study period, with the remaining patients classified as non-users. Classified statin use by the type of statin first prescribed.

Calculated the number needed to treat to benefit one patient (**NNT**) and the number needed to treat to harm one patient (**NNH**) over 5 years for patients at high risk of cardiovascular disease. It was based on a QRISK2 score indicating a risk of 20% a CVD event over the next 10 years, the group eligible for statin treatment in the UK.

. Included 368 practices with a total of 2 121 786 patients age 30-84 at study entry:

1 778 770 had not been prescribed statins: 225 992 were new users. The majority

received simvastatin. The remainder received: atorvastatin, fluvastatin, pravastatin and rosuvastatin.

The associations between statins and Parkinson disease; rheumatoid arthritis; venous thrombo-embolism; gastric, lung, renal, breast and prostate cancers; and melanoma were not significant.

Adverse effects significantly associated with statins:

Cataracts, moderate or serious liver dysfunction, acute renal failure, and myopathy:

Beneficial effects significantly associated with statins:

Cardiovascular disease and esophageal cancer:

Numbers needed to treat to *benefit* one patient (NNT) over 5 years:

Women	NNT	No per 10 000
CVD Event	37	271
Esophageal cancer	1266	8
Men		
CVD event	33	301
Esophageal cancer	1082	9

Numbers needed to treat to *harm* one patient (NNH) over 5 years:

Women	NNH	No. per 10 000
Cataract	33	307
Liver dysfunction	136	74
Myopathy	259	39
Acute renal failure	434	23
Men		
Cataract	52	191
Myopathy	91	110
Liver dysfunction	142	71
Acute renal failure	346	29

All risks persisted during treatment and were highest in the first year of treatment. After stopping treatment, risks returned to normal within 1 to 3 years, except for myopathy, which did not abate.

Adverse effects tended to be similar across all types of statins. The risk of liver dysfunction was highest with fluvastatin. The risk of liver dysfunction, acute renal failure, and possibly myopathy were dose-related. As liver dysfunction is common and the other two outcomes are life threatening, the

findings tend to support a policy of using lower doses of statins in people at high risk for the adverse effects.

This study adds important data. The large data-base increases validity and generalizability.

We need to know how common adverse effects of statins are. The list of diseases not associated with statins is reassuring, as is the observation that risk returns to normal after a year or two.

Statins are among the safest drugs we use. They are not innocuous. In general,, over a 5-year period, between 2 in 1000 and 11 per 1000 will be harmed. For cataracts, the harm is up to 3 per 100. We must be alert for these effects. (This is my first encounter with the risk of cataracts associated with statins.)

At some point, depending on individual risk of CVD, harm may outweigh benefit. This may occur in the very young and the very old.

Drug companies tout the strength of their statins, stating that they reduce LDL-cholesterol more than their competitors. Pushing the dose to obtain lower LDL-c levels may increase adverse effects. I believe “go slow and go low”, while observing the effect, applies to statins.

SWEETENERS

Increased Fructose and Sucrose Intake is Associated with Dyslipidemia

4-7 CALORIC SWEETENER CONSUMPTION AND DYSLIPIDEMIA AMONG US ADULTS

In the US, total consumption of sugar has increased substantially in recent decades largely due to an increased intake of “added sugars”, defined as caloric sweeteners used by the food industry and consumers as ingredients of processed and prepared foods. Today, the most commonly added sugars are refined beet or cane sugar (sucrose) and high fructose corn syrup.

This study assessed the association between consumption of added sugars and lipid levels in US adults.

The cross-sectional study among non-institutionalized US adults (n = 6113; half women, half men) assessed data from the National Health and Nutrition Examination Survey (NHANES) 1999-2006. The study obtained nationally representative estimates of diet and health indicators.

Determined nutrient content of foods consumed by use of US Department of Agriculture National Nutritional Database and the My Pyramid Equivalents Database. Added sugars were determined from 337 different foods.

Determined the intake of added sugars for each respondent, and the % of energy intake (kcal) from added sugars.

The mean of self reported weight gain was 2.8 pounds among those with 25% or greater total energy from added sugars compared with a mean loss of 0.3 pounds among those whose total intake of added sugars was less than 5%.

Total energy intake increased as the proportion of energy from added sugars increased from 5% of total energy to 25% or greater.

Outcomes (means)	% of added sugars	
	5%	25%
HDL (mg/dL)	59	48
TG	105	114
TG/HDL	2.4	3.1
LDL (women)	116	122 (Estimates fro fig 3 p 1495)
(men)	No difference	

(The authors offer no explanation for this.,)

Odds ratios	% of added sugars	
	5%	25%
Low HDL	1.00	3.1 (< 40 mg/dL men; < 50 women)
High TG (150)	1.00	1.2
High LDL (>130)	1.00	1.2
High TG/HDL (>3.8)	1.00	1.6 (Estimated from a model adjusting for multiple possible confounding factors.)

Individuals in this study consumed an average of about 16% (one sixth) of their daily calories from added sugars. This represents a substantial increase from 1977 when added sugars contributed only about 11% of the calories consumed by adults.

“Our results support the importance of dietary guidelines that encourage consumers to limit their intake of added sugars.”

Conclusion: Higher consumption of added sugars was associated with several important measures of dyslipidemia. The data support dietary guidelines that target a reduction in consumption of added sugar.

TOBACCO

“There Is No Safe Dose Of Tobacco Smoke”

2-4 TOBACCO SMOKE BY ANY OTHER NAME IS STILL AS DEADLY [Editorial]

Data show that, although cigarette consumption has declined substantially, consumption and sales of other tobacco products, most notably cigars, has increased.

“We are still trying to convince the public that these products are not safe alternatives to cigarettes.”

A study in this issue of *Annals* reports that smokers of pipes and cigars have substantial nicotine absorption as well as measurable lung damage. The results are especially important because the tobacco industry is actively promoting product substitution and use as an alternative to complete cessation.

Some believe that smoke from these products is not inhaled at all, contributing to misguided perceptions of reduced harm. In fact, pipe and cigar smokers do inhale, especially former cigarette smokers.

The study showed that smokers of these products are exposed to sufficient levels to affect their pulmonary health. The measured reduction in pulmonary function clarifies the substantial harm. Self-reported current pipe and cigar smokers had elevated cotinine levels compared with never-smokers. Pipe-years were associated with decrements in FEV1. Cigar-years were associated with decrements in FEV1/FVC ratio. Both groups had increased odds of airflow obstruction. Whether or not they had smoked cigarettes (odds ratio = 3.4) or not (odds ratio = 2.3) compared with participants with no smoking history.

Other studies have reported that cigar and pipe smokers, compared with non-smokers, have higher risk of cardiovascular disease (RR = 1.22), COPD (RR = 1.45), lung cancer (RR = 2,14), and overall mortality (RR = 1.44).

Life-years lost have been estimated at 5 years compared with cigarette smokers 7 years.

As changes in public health policy have made cigarettes less socially acceptable, a distinct set of characteristics are associated with cigar and pipe use: sophistication, affluence, education, and celebration. These images, largely fostered by the tobacco industry, perpetuate the idea that these products play a suitable role in our society.

URINARY TRACT INFECTION

“Highlights the Tension between Maximizing the Benefit For Individuals and Minimizing Antibiotic Resistance”

2-1 URINARY TRACT INFECTION IN PRIMARY CARE

(This editorial comments on a study presented in this issue of BMJ. I added comment from 4 shorter articles in the same issue. Please read the full abstract. RTJ)

On the face of it, urinary tract infections (UTI) seem to be a straight forward clinical presentation, with an equally straightforward treatment response. Bacterial infection is more likely to be present

than not, and empirical treatment is effective.

The problem with empirical treatment of UTI is that 10% of the healthy adult female population would receive antibiotics each year. This has implications for antibiotic resistance.

Research in this area focuses on strategies to reduce use of antibiotics. “This highlights the tension between maximizing the benefit for individuals and minimizing antibiotic resistance at a population level.”

In studies of UTI, diagnosis, treatment and cure were traditionally defined in bacteriological, rather than in symptomatic terms, on the assumption that people with detectable infection would benefit, whereas people without infection would not. However, evidence indicates that many women with bacteriological UTI will recover without antibiotics. In addition, about one third of women who present with clinically identical symptoms of UTI do not have detectable bacteriological infection, but do have a symptomatic response to empirical antibiotics.

An open, parallel, randomized controlled trial presented in this issue of BMJ computed five treatment permutations for uncomplicated UTI:

- 1) Empirical immediate antibiotics.
- 2) Empirical delayed antibiotic. (Prescription to use after a delay of 48 hours if necessary,)
- 3) Treatment based on a clinical test algorithm. (Two or more of cloudy urine, smelly urine, nocturia, dysuria).
- 4) Treatment based on a dipstick test algorithm. (Nitrites, leucocytes, and blood).
- 5) Treatment based on urine culture results.

[3), 4), and 5) also provided delayed prescriptions]

There were no statistically significant differences in duration or severity of symptoms with any of the approaches. Women had 3.5 days of moderately-bad or worse symptoms even if they took antibiotics immediately.

Duration of symptoms was shorter when the doctor was perceived to be positive about diagnosis and prognosis.

There were differences in use of antibiotics (range 77% for dipstick to 97% for immediate prescription). But this was offset by an increase in symptom duration when antibiotics were delayed by 48 hours, particularly in the urine culture arm. Patients who waited at least 48 hours to start antibiotics reconsulted less, but on average had symptoms for 37% longer than those taking immediate antibiotics.

The proportion of symptomatic women with no identifiable bacteriological infection (36%) was similar to that found in previous studies

“Women with signs/symptoms of urinary tract infection prefer to avoid taking antibiotics.” They valued the opportunity to avoid unwanted side-effects associated with antibiotics.

But most women presenting with UTI in primary care are prescribed an antibiotic. Overall, in this cohort, only 9% took no antibiotics.

The patient's situation and preference determine which approach will probably be the most helpful.

Delayed empirical prescription or dipstick guided delayed options will reduce the likelihood of taking antibiotics. But delaying antibiotics by 2 or more days increases the risk that more severe symptoms will be prolonged.

In an age of protocols and targets, the way a doctor provides care can enhance the effectiveness of treatment. Preoccupation with diagnosis and therapeutic goals obscure the wider aspects of therapeutic influence.

The clinician needs to address the particular worries that women might have and explain the rationale for not using antibiotics immediately.

I enjoyed abstracting these studies in detail. They present an extremely common complaint in primary care, and the difficult decisions to make, both for the clinician and the patient.

I believe they do provide some guidance. A reasonable approach would be to do a quick dipstick:

If negative, the patient may be more inclined to delay antibiotics and receive symptomatic therapy.

If positive, a discussion may follow with treatment based on the patient's perception of the severity of pain and willingness to delay antibiotics for a day or two, or to avoid them completely.

As usual, personal informed decision-making takes precedence, including past history and severity of symptoms.

Note that about 90% of the women in these studies eventually received an antibiotic.

VASCULAR DISEASE

3-1 ASPIRIN AS PREVENTIVE THERAPY IN PATIENTS WITH ASYMPTOMATIC VASCULAR DISEASE [Editorial] See under ASPIRIN

VENOUS THROMBOEMBOLISM

Superficial Venous Thrombosis Is Not Benign

2-6 SUPERFICIAL VENOUS THROMBOSIS AND VENOUS THROMBOEMBOLISM

This study enrolled 844 patients (mean age = 61; 21% over age 75; women 65%) with symptomatic SVT of the lower extremity, defined as a subcutaneous non-compressible hypoechoic area in the course of an identified superficial vein (appearing circular in cross-sectional view, and

rectangular in longitudinal view) more than 5 cm in length on compression ultrasonography.

Determined the prevalence of DVT or symptomatic pulmonary embolism (**PE**) in patients with a diagnosis of SVT at presentation.

Followed patients with SVT-alone (without DVT or PE at presentation) for 3 months to assess TE complications. All received a second ultrasound of both lower limbs within 2 weeks, and an assessment of symptomatic events at 3 months.

Of the 844:

- a. 210 (25%) had DVT or symptomatic pulmonary embolism (4%) at inclusion.
- b. 634 had SVT-alone. Of these, the study followed 586 for 3 months.

Of the 586 with SVT alone: (without DVT or PE at inclusion) 58 developed thromboembolic complications by 3 months:

Symptomatic	Number
Pulmonary embolism	3 (one probable death)
DVT	15
Extension of SVT	18 (despite almost all receiving anticoagulants)
Recurrence of SVT	10
Asymptomatic	12

Almost all received anticoagulation. Other treatment: compression stockings (98%); topical and oral NSAIDs (55%); venous surgery (stripping or ligation 10%)

“In our large observational study, we found that venous thromboembolism accompanied symptomatic SVT in nearly 25% of patients.”

In patients with isolated SVT at inclusion, 8% developed at least one thromboembolic event

at 3 months:	%
Symptomatic DVT	3
Pulmonary embolism	0.5
Symptomatic extension of SVT	3
Symptomatic recurrence of SVT	2

Conclusion:

Symptomatic SVT of the lower extremities is *not* benign. Many patients have complications at presentation. Others are at risk of complications within 3 months.

Compression ultrasonography might be considered for patients with symptomatic SVT at presentation.

Close follow-up of patients with isolated SVT might be advisable.

SVT is not an innocuous disease. At a 25% rate of DVT and 4% PE at presentation, it approaches a medical emergency. Primary care clinicians should consider early anticoagulation.

Patients presenting with varicose veins also deserve urgent care. Not only for cosmetic reasons. Early referral for surgery may be warranted.

VITAMIN B-12

See under DIABETES “5-5 LONG TERM TREATMENT WITH METFORMIN IN PATIENTS WITH TYPE-2 DIABETES AND RISK OF VITAMIN B-12 DEFICIENCY”

VITAMIN D

“Association Does Not Prove Causality”

1-1 DIAGNOSIS AND MANAGEMENT OF VITAMIN D DEFICIENCY

In recent years, non-musculoskeletal conditions have been found to be associated with low vitamin D (**D**) levels: cancer, metabolic syndrome, infections, and autoimmune disorders.

D deficiency is widespread. Rickets represents a small proportion of individuals with suboptimal D status. A recent nationwide survey in the UK showed that more than 50% of adults have insufficient levels and 16% have severe deficiency in winter and spring. Greatest deficiencies are in more northern latitudes, in the elderly, obese individuals, and blacks,

This review is based on evidence from descriptive and observational studies, randomized trials, and meta-analyses. It discusses:

Sources of D

How can D deficiency and insufficiency be determined?

Who is at risk of D deficiency and insufficiency?

How do patients with D deficiency present?

What investigations are necessary?

How should osteomalacia be treated?

How should moderate deficiency be managed?

Conclusion: D deficiency and insufficiency is common. Health professionals have been slow to respond. Rickets and osteomalacia are entirely preventable. Deficiency now seems unequivocally linked to several other common and morbid conditions.

“We have some way to go.” A change in public health policy in the UK is overdue.

Please read the full abstract.

Practical Pointers has abstracted a number of articles about vitamin D. I enjoyed this overview.

The various diseases putatively related to D need strict verification. Does deficiency really cause them? Association does not prove causality. If it turns out that deficiency is causal this would be a major advance.

Would it not be refreshing to have a major advance in therapeutics, which costs pennies, and is harmless?

The usual protocol in medicine is to test for deficiencies, then treat those who are deficient. When large numbers of the population are afflicted, is there not a good argument to treat everyone without checking for deficiency, provided the therapy is low-cost and low-harm. We do not check patients for deficiency of antibodies to flu, tetanus and other infections before giving vaccines.

I grew up in the cod-liver-oil generation (1920-30). The reason was to prevent rickets. In hindsight, it probably brought more benefits.

D Alone Does Not Reduce Risk Of Fracture. Add Calcium

1-2 PATIENT LEVEL POOLED ANALYSIS OF 68 000 PATIENTS FROM SEVEN MAJOR VITAMIN D FRACTURE TRIALS IN US AND EUROPE

This study used individual patient data in a meta-analysis of randomized, controlled trials of D--with and without calcium-- in preventing fractures.

Literature search from 1966 to 2008 found 7 major randomized trials comparing D + calcium vs placebo, and D alone vs placebo, yielding a total of over 68 000 participants (mean age 70; 85% women). Analysis was at the level of individual patients according to intention-to-treat principle.

Effect of D (with and without calcium):

A. Any fracture (n = 7202; 170 000 person-years) hazard ratios (**HR**) vs placebo:

	HR (vs placebo)
D alone	1.01 (No effect)
D + calcium	0.92
Injected D	1.11 (No effect)
Oral D	0.92

B. Hip fracture (n = 978)

	HR
D alone	1.09 (No effect)
Calcium + D	0.84

Absolute risk reduction of fractures and number needed to treat over 3 years

(This was analyzed only for calcium + D, as D-alone provided no benefit.)

	ARR	NNT
Any fracture	0.5%	213
People over 70	0.9%	111
People with previous fracture	1.2%	82
Hip fracture (over age 70)	0.4%	255

Whether calcium is more important in preventing fracture than was previously recognized remains to be determined. But calcium + D is more likely to be more effective in attenuating secondary hyperparathyroidism and bone turnover than D alone.

“Our recommendation would be to use a vitamin D dose of at least 400 IU daily combined with 1000 mg calcium.” In high risk patients this should be supplemented by bisphosphonates or other anti-osteoporotic drugs.

Conclusion::

Vitamin D alone was not effective in preventing fractures

Calcium and vitamin D given together reduced hip fracture and total fractures irrespective of age, sex, or previous fractures.

Daily calcium and vitamin D supplementation, even at doses as low as 400 IU + 1000 mg calcium daily, significantly reduced the risk of fracture. Incidence curves (vs placebo) deviated after about 15 months.

I enjoyed this article. It presents an important intervention in primary care.

Primary care clinicians will appreciate the authors' calculations of absolute risk reductions and the NNT. This will allow presentation of a clearer picture of benefits and costs to patients.

The benefit / harm-cost of D3 + calcium is very high. Fractures are costly and disabling, and sometimes fatal. The cost of daily calcium-D pills is very low (~ 7 cents). Harm is nil. This, I believe, will lead many patients to choose this intervention.

Benefit to society is also high.

I believe clinicians in the US often prescribe higher doses of D--1000 to 2000 IU daily.

Is D Going The Way Of Antioxidants And Folic Acid?

3-6 VITAMIN D SUPPLEMENTATION IN THE AGE OF LOST INNOCENCE [Editorial]

Two systematic reviews and editorial comment update the present status of the association between D and cardiovascular disease, diabetes, hypertension, and mortality. *(Please read the full abstract. RTJ)*

Some observations::

The widespread claims of health benefits of D from increased intake follow decades of research that led to the collapse of similar claims regarding antioxidant vitamins and folic acid supplementation. Will history repeat itself?

For clinical CVD outcomes, 4 of 7 analyses found that low blood concentrations of D were associated with increased risk. For incident diabetes, 3 of 6 analyses found low D status associated with increased risk. For both clinical cardiovascular and diabetes outcomes, the methods of the original studies were too heterogeneous to consider pooling. For hypertension, 3 cohorts reported that low D concentrations were associated with an overall 79% increase in the odds of incident hypertension.

Evidence from limited data suggests that vitamin D supplements at moderate to high doses may reduce CVD risk. Generalizability is uncertain. Further research is needed.

Two randomized trials reported no significant effect on risk of ischemic heart disease or stroke. There was a significant reduction in fractures.

A meta-analysis of 18 trials found that D supplementation was associated with a reduced all-cause mortality by 7%.

Observational studies may be subject to various biases for estimating the effect of vitamin and mineral supplementation on disease endpoints.

The editorialist concludes:

“The effect of vitamin D supplements on cardiovascular disease, diabetes, and hypertension remains uncertain. However, the available evidence in favor of vitamin D supplementation is far more promising than for other vitamin or mineral supplements.”

From a biological perspective, the presence of D receptors in many cell types and organs support the potential broad-ranging effects of D.

“We believe that the evidence for widespread use of high dose vitamin D supplementation in the general population remains insufficient.”

Trials of antioxidant vitamins have taught us that we cannot anticipate small risks of presumed safe interventions that, when applied to hundreds of millions of persons, could result in thousands of detrimental events.

We must define the optimal dose, and the real benefits and potential harmful effects of supplementation. Enthusiasm for supplementation must be tempered by the loss of innocence from trials of antioxidant supplements that showed not only benefits, but also harms.

“Conducting large randomized trials of high-dose vitamin D should be a public health priority.”

What do we understand at this time?

D deficiency is common

Replacement to normal levels seems reasonable

Replacement does reduce risk of falls and fractures, especially in the elderly, resulting in a reduction in mortality

Evidence of benefit is conflicting

Long-term harms when large numbers of persons receive moderately high doses is not known

We must wait for a definitive answers

Questions:

Must we wait until blood levels reach normal levels before judging benefits and harms?

Who will conduct a very large RCT? Certainly not the drug companies. There would be no profit.

I believe many individuals will continue to take moderately high doses of D. The putative benefit / harm-cost ratio is high.

WEIGHT GAIN

“Weight Gain Experienced By A Typical American Must Be Caused By Repeated Changes In Diet, Physical Activity, or Both”

1-3 EXTRA CALORIES CAUSE WEIGHT GAIN--BUT HOW MUCH?

How much would an individual gain by eating an extra chocolate chip cookie every day for life?

One approach to answering this question is based on the assumption that a pound (454 g) of fat tissue has about 3500 kcal. Thus, a daily 60 kcal cookie would be expected to produce 0.5 lb weight gain a month, 6 lb in a year, 60 lb in a decade, and hundreds of pounds in a lifetime.

Of course, this does not happen.

This article reviews the physiology of weight gain and loss. And the amount of reduction in caloric intake necessary to avoid becoming overweight and obese.

WEIGHT CHANGE IS SELF-LIMITING

When energy intake increases above expenditure, the excess is used to build new tissue, and weight gain results. However, weight gain does not continue indefinitely. Calorie expenditure increases progressively because of the energetic costs of maintaining the newly created tissue. A person who consumes an extra cookie every day will initially gain weight, but over time an increasing proportion of the cookie's calories will go into repairing, replacing, and carrying the extra body tissue. After a few

years of daily cookie eating, weight gain will level off at approximately 6 lbs. Thus, a one-time step up in caloric intake will cause body weight to increase to a new stable level.

The converse occurs when an individual reduces food intake. As body size diminishes, so does the amount of fuel needed to maintain and move it. Weight settles to a new steady level.

1) To prevent weight gain as you age:

As you age, physical activity lessens. If your weight is increasing, cut calories and/or increase physical activity

As you later hit a weight plateau, you have to take a further step to reduce caloric intake and/or increase activity

You may have to make several adjustments over the years to prevent gain.

2) To lose weight:

Cut calories and increase physical activity

When you hit a plateau, you may have to cut calories further and/or increase physical activity

You may have to make several adjustments to continue losing weight.

Americans have the habit of overeating and gaining weight during holidays. They make no adjustment to subsequently lose the weight. Weight increases cumulatively.

