This index is a reference document based on articles abstracted from 6 flagship journals January – June 2009. It provides a means of recalling to memory, in an evening or two, what the editor considered new and important for primary care.

The numbers in the brackets refer to the abstract. For example, [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 44 medical subject headings from Alzheimer’s disease to whooping cough, 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 Mediocine.

4) The abstract itself 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 2009

ADVISE
Use aspirin for secondary prevention of vascular disease. Use in primary care is debatable [5-3]
Avoid inhaled long-acting beta-agonists alone for asthma. Use combined with inhaled corticosteroids [1-5]
Body-mass-index is 22.5-25 is the most favorable for longevity [3-1]
Reduce risk of hypertension by increasing potassium intake and decreasing sodium intake to [1-1]
Physicians to read “The Science of Care”—Caring for the Patient [4-1] And “Humanism in Medicine” [6-1]
Testing for celiac disease in patients with irritable bowel syndrome [4-4]
Life-style factors to reduce onset of type-2 diabetes, even in older patients [[6-3]
Physicians to promptly advise patients of clinically significant outpatients test results [6-2]
Avoiding NSAIDs in patients with heart failure [1-3]
Patients to self-monitor BP [2-9]
Patients to reduce meat and meat products intake to reduce cancer, CVD, and total mortality [3-4]
Pneumonia vaccine for smokers [1-9]
Patients that modest and achievable health behaviors will reduce incidence of stroke [3-5]
Obese patients that weight loss may reduce prevalence of urinary incontinence [1-4]
Adequate supplementation with vitamin D may reduce incidence of upper respiratory disease as well as other conditions. Patients need supplementary vitamin D [2-1]

CONSIDER
Aspirin continues to be underused for prevention of CVD [3-3]
In patients with atrial fibrillation, clopidogrel added to aspirin slightly lowers risk of major vascular events, but increases risk of major bleeding. [5-2]
Monitoring bone mineral density by DXA during first 2 to 3 years of antiresorptive drug treatment may be potentially misleading and wasteful [6-4]
Antidepressants may be associated with improvement in patients with fibromyalgia [1-6],
Testing more patients for HIV. Rapid saliva testing is highly sensitive and specific [1-7]
Asking whether screening for prostate cancer with PCA does more harm than good [3-6]
Financial incentives may reduce prevalence of smoking [ 2-8]
Vitamin D for patients with type-2 diabetes and neuropathic pain [4-7]
BE AWARE

There is a new test for memory [6-11]

Aspirin may prevent cardiovascular disease in patients with peripheral vascular disease. The benefit may be small. [5-4]

A large gap persists between the standards set for CVD prevention and actual usage in the community. We should do better [3-2]

When patients are required to meet higher co-payments for drugs they may not take the drug [4-2]

There are continuing doubts about the benefit/harm ratio of tight glucose control on macrovascular complications in patients with type-2 diabetes. A reasonable HbA1c is 7%. Lipid, weight, and BP control are more important [1-8] [4-5]

Prevalence of prediabetes in the US is high. Public awareness is low. This is a challenge and opportunity for primary care [2-6]

HbA1c may become the preferred test for diagnosis of diabetes. [4-8]

Behavioral factors, rather than the exact type of diet are the main influence on weight loss [2-2]

Physicians share responsibility with patients for difficult encounters [2-4] [2-5]

Human quadrivalent human papilloma vaccine is efficacious in women age 24-45 [6-5]

“Normal” BP cutpoints of 140 and 130 are artificial. Patients may benefit when BP is lowered below 130 and below 120 [5-1]

Of some new developments in hyperthyroidism [6-10]

Interest in the “polypill” continues. It may reduce multiple risk factors for CVD [4-3]

That stopping smoking, a leading cause of death, could result in making COPD and lung cancer relatively uncommon [2-7]

Vitamin D serum levels may be undetectable in elderly sick patients. Mortality is increased [4-6]

There is a new diagnostic test for pertussis—antibody to pertussis toxin in oral fluid. It is 99% specific [3-6]

You can keep up to the minute on the flu pandemic through the internet (eg, Google)
ALZHEIMER'S DISEASE
ASPIRIN
ASTHMA
ATRIAL FIBRILLATION
BODY-MASS INDEX
BONE MINERAL DENSITY
CARDIOVASCULAR DISEASE
CARDIOVASCULAR RISK ASSESSMENT
CARING FOR THE PATIENT
CELIAC DISEASE
CLOPIDOGREL
COGNITIVE SCREENING TEST
CO-PAYMENTS
CORONARY HEART DISEASE
DIABETES
DIET
DIFFICULT ENCOUNTERS IN PRIMARY CARE
FAILURE TO INFORM PATIENTS
FIBROMYALGIA
GUIDELINES
HEART FAILURE
HUMAN IMMUNODEFICIENCY SYNDROME (HIV)
HUMAN PAPILLOMA VIRUS (HPV)
HUMANISM IN MEDICINE
HYPERTENSION
HYPERTHYROIDISM
INFLUENZA
IRRITABLE BOWEL SYNDROME
MEAT INTAKE AND MORTALITY
NSAIDS
OBESITY
OSTEOPOROSIS
PERIPHERAL VASCULAR DISEASE
PNEUMONIA VACCINE
POLYPILL
PREDIABETES
PROSTATE CANCER
SCREENING TEST FOR COGNITION
SMOKING
STROKE
TEST YOUR MEMORY
URINARY INCONTINENCE
VASCULAR DISEASE
VITAMIN D
WHOOPING COUGH
ALZHEIMER’S DISEASE

*A Positive And Valid Screening Test For The Detection Of AD*

6-11 SELF ADMINISTERED COGNITIVE SCREENING TEST (TYM) FOR DETECTION OF ALZHEIMER’S DISEASE

Three requirements for widespread use of cognitive tests for use by non-specialists:

1. Minimal operator time to administer
2. Test a reasonable range of cognitive functions
3. Sensitive for Alzheimer’s disease (AD)

The TYM (“test your memory”) test was designed to fulfill these requirements.

The test is a series of 10 self-administered tasks: orientation, ability to copy a sentence, semantic knowledge, calculation, verbal fluency, similarities, naming, visiospatial abilities, and recall of a copied sentence. Perfect score = 50

A cross sectional study included 94 patients with AD attending a memory clinic, 23 patients with amnestic mild cognitive impairment, and 540 controls.

Controls: Average score was 47 of 50 for ages 18-70. Scores slightly declined after age 70, and significantly declined after age 80.

AD patients: Average score was 33 of 50

With a cut-point of 42 or less, the TYM detected 93% of patients with AD; the MMSE at the established cut point of 23 or less detected 52%.

Patients with mild cognitive impairment averaged 29 of 30 on the MMSE and 45/50 on the TYM. They tended to score worse on anterograde memory.

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I abstracted this article to note that a substitute for the MMSE is available. Use of the MMSE is constrained by a copyright.

The TYM is designed as a quick screening test for primary care. www.tymtest.com

There are several cognitive tests available. They seem similar. More time may be needed to establish the place of TYM—its limitations and usefulness in English-speaking societies

ASPIRIN

“Aspirin Continues To Be Underused”

3-3 ASPIRIN FOR PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASE

Some fundamental questions about prophylactic use of aspirin remain unanswered. Two key questions are:
1) What is the optimum dose for treatment of established cardiovascular disease (secondary prevention)?

2) In whom and when should aspirin be used for prevention of cardiovascular events in persons with no history of cardiovascular disease (primary prevention)?

The large Antithrombotic Trialists’ Collaboration meta-analysis (ATC; 2002) of patients at high risk found that antiplatelet therapy (chiefly aspirin) reduced the risk of serious vascular events by 1/4; non-fatal MI by 1/3; non-fatal stroke by ¼; and vascular mortality by 1/6. (Secondary prevention.)

The combined evidence from aspirin trials is compelling, and has led to the universal recommendation of aspirin as standard therapy in patients with established vascular disease.

The benefit of aspirin is no greater with high doses than with low doses (75-150 mg). Higher doses do not lead to improved efficiency, and may be associated with more bleeding.

In this issue of Annals, the US Preventive Services Task Force (USPSTF) updates its recommendations for aspirin in primary prevention of coronary heart disease

USPSTF encourages use of aspirin:

1) For men age 45 to 79 when the potential benefit of a reduction in MI outweighs the potential harm of GI hemorrhage.

2) For women age 55 to 79 when the potential benefit in reduction of stroke outweighs the potential harm of GI hemorrhage.

The USPSTF guidelines do not recommend aspirin for men under age 45, or for women under age 55.

It could be argued that aspirin should be used in all individuals, men and women, who have a reasonable risk of a major cardiovascular event.

A valuable feature of USPSTF is the recommendation to share decision-making with the patient, discussing the benefits and risks, and individualizing decisions to the specific patient or situation.

“Aspirin continues to be underused, and the incorporation of the USPSTF’s recommendations into daily practice will increase the use of aspirin and, in turn, prevent many thousands of cardiovascular events every year.”

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The Women’s Health Study (WHS; 2005) was somewhat contrary. It randomized aspirin 100 mg every other day vs placebo for a mean of 10 years in over 39,000 women age 45 and older (mean age 55). Unexpectedly, aspirin did not reduce risk of myocardial infarction or death. The risk of ischemic stroke declined by 24%, with a non-significant increase in risk of hemorrhagic stroke.
As usual, decisions to use aspirin depend on agreement between clinicians and patients who are fully informed about benefits and harms.

For details about the ATC and the Women’s study go to Google:

PMID: 11786451  PMID: 15753114

5-2  EFFECT OF CLOPIDOGREL ADDED TO ASPIRIN IN PATIENTS WITH ATRIAL FIBRILLATION

This study assessed whether clopidogrel + aspirin would reduce risk of thromboembolic stroke and other major vascular events in patients with AF to a greater degree than aspirin alone. And whether clopidogrel + aspirin would lead to greater risk of hemorrhage.

A double-blind, randomized trial in 580 centers in 53 countries followed over 7500 patients with AF (mean age 71). All subjects had AF at entry or had at least two episodes of AF in the past 6 months. They were considered “unsuitable” for warfarin therapy.

Randomized to: 1) aspirin (75-100 mg daily) + placebo (aspirin-alone), or 2) clopidogrel (Plavix; Bristol Myers Squib; 75 mg daily) + aspirin . (C + A)

Primary outcome = combination of stroke, myocardial infarction, non-CNS systemic embolization, or death from vascular causes.

<table>
<thead>
<tr>
<th>Outcomes (% per year)</th>
<th>C + A</th>
<th>Aspirin-alone</th>
<th>Absolute difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>6.8</td>
<td>7.6</td>
<td>0.8</td>
<td>125</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>1.9</td>
<td>2.8</td>
<td>0.9</td>
<td>111</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.2</td>
<td>0.2</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Disabling or fatal stroke</td>
<td>1.6</td>
<td>2.1</td>
<td>0.5</td>
<td>200</td>
</tr>
</tbody>
</table>

Risks of hemorrhage (%/y):

<table>
<thead>
<tr>
<th></th>
<th>C + A</th>
<th>Aspirin-alone</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major bleeding</td>
<td>2.0</td>
<td>1.3</td>
<td>143</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>3.5</td>
<td>1.4</td>
<td>47</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0.4</td>
<td>0.2</td>
<td>500</td>
</tr>
</tbody>
</table>

The addition of clopidogrel to aspirin (as compared with aspirin alone) reduced the rate of major vascular events from 7.6% per year to 6.8% per year, primarily due to a reduction in stroke. (NNT for one year to prevent one major vascular event = 125; to prevent one stroke = 111. One in 143 will experience a major hemorrhage.)

“It is important to emphasize that oral anticoagulation with a vitamin K antagonist is the preferred and recommended therapy for the prevention of ischemic stroke in patients with atrial fibrillation.”

Use of C + A did not result in a significant reduction in mortality from any cause. The majority
of deaths in this study were due to arrhythmia, heart failure, and non-vascular causes.

Conclusion: In patients with AF for whom warfarin therapy was “unsuitable”, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage.

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Plavix is widely advertised directly to the public. It is expensive. My drug store quotes a price of $4.77 for one 75 mg tablet. To reduce the occurrence of one major vascular event over 1 year, 125 patients must be treated with C + A vs aspirin-alone; 124 will take the drug without benefit. Each will be exposed to adverse effects and a cost of $1,741.00 yearly.

The yearly cost of prescribing Plavix to the 124 patients (and to society) who will not benefit will be $215,884.00. Caring for the additional patients who have major bleeding when taking Plavix adds to the cost.

The benefit / harm –cost ratio of Plavix is very low.

Whether to use warfarin, clopidogrel, aspirin, or a combination of clopidogrel + aspirin in patients with AF is a high-risk decision. Patients must be fully informed about benefits, adverse effects, and cost before making their personal judgment.

Primary care clinicians are in a no-win situation when prescribing anticoagulants and anti-platelet drugs for AF. If the patient does not experience a thromboembolic stroke, there is no way of determining whether the drug prevented it. If the patient experiences a major bleeding episode, the physician will blame herself, and the patient will blame the physician and the drug.

Should Be Used for Secondary Prevention. Use for Primary Prevention Is Debatable.

5-3 ASPIRIN IN THE PRIMARY AND SECONDARY PREVENTION OF VASCULAR DISEASE

A Collaborative Meta-Analysis Of Individual Participant Data From Randomized Trials

Long-term, low-dose aspirin is of definite and substantial benefit for many people who already have occlusive vascular disease and are at high risk for recurrence. (Secondary prevention)

For secondary prevention, benefit of aspirin substantially exceeds the risk of bleeding.

For primary prevention, the balance is less clear. The absolute benefits in primary prevention are generally on order of magnitude lower than in secondary prevention.

Current guidelines largely ignore any differences in bleeding risk and recommend that aspirin be used widely for primary prevention in those at moderately raised risk for coronary heart disease (CHD).
In this meta-analysis, primary prevention trials were eligible only if they involved a randomized comparison of aspirin vs no aspirin. Persons with any history of occlusive vascular disease and diabetes were excluded. Six primary prevention trials (95 000 persons) were included.

Secondary prevention trials included individuals with previous myocardial infarction, stroke, or transient ischemic attack (16 trials; 17 000 persons) that compared long-term aspirin vs controls.

Yearly absolute difference (% per year aspirin vs control):

<table>
<thead>
<tr>
<th>Event</th>
<th>Primary prevention</th>
<th>Secondary prevention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major coronary event</td>
<td>-0.06 %</td>
<td>-1.00 %</td>
</tr>
<tr>
<td>Non-fatal MI</td>
<td>-0.05</td>
<td>-0.66</td>
</tr>
<tr>
<td>CHD mortality</td>
<td>-0.01</td>
<td>-0.34</td>
</tr>
<tr>
<td>Stroke</td>
<td>-0.01</td>
<td>-0.46</td>
</tr>
<tr>
<td>Vascular death</td>
<td>-0.01</td>
<td>-0.29</td>
</tr>
<tr>
<td>Any serious vascular event</td>
<td>-0.07</td>
<td>-0.29</td>
</tr>
<tr>
<td>Major extracranial bleed</td>
<td>+0.07</td>
<td>a</td>
</tr>
</tbody>
</table>

(a. Extracranial bleeding incompletely reported.)

Primary prevention trials: The NNT (number needed to treat to benefit one patient over one year) varied from 1111 to 10 000. The number needed to treat to harm (NNTharm) one primary prevention patient per year (major hemorrhage) = 1428.

Secondary prevention trials: The NNT to benefit one patient per year varied from 100 to 344—about ten times the benefit in primary prevention. *(I assume the bleeding complications (NNTharm) were comparable to those in primary prevention trials. RTJ)*

In the primary prevention trials, the absolute risk of a serious vascular event among people of a given age and sex was an order of magnitude less than in secondary prevention trials.

In primary prevention, the absolute reduction in occlusive events would be only about twice as large as the absolute increase in bleeding. Moreover, these trials of aspirin were mainly in people who were not taking statin therapy, which would have reduced both myocardial infarction and ischemic stroke with little hazard.

There is still a possibility that there is some particular category of individuals in whom primary prevention with aspirin is of definite benefit. Adults with diabetes may benefit more.

Even in people at moderately increased risk of CHD, the absolute benefits and harms of adding aspirin to a statin-based primary prevention regimen could still be approximately evenly balanced.
Conclusion: For primary prevention in persons without previous vascular disease, aspirin is of uncertain net value. Reductions in occlusive events should be weighed against the increased risk of major bleeding. For secondary prevention, benefits of long-term aspirin outweigh risks.

I recall when the US Physicians’ Health Study was published (1988), many persons including many physicians began to take low-dose aspirin daily. Since then, some of the bloom has come off this application. But many people still take aspirin for primary prevention. And many guidelines advise it for certain groups (eg, diabetes).

Secondary prevention should continue routinely.

The decision for primary prevention is up to the individual patient’s preference after full explanation of possible harms and benefits. The chief message of the study was to point out harms as well as benefits. Patients should be so informed.

Other risk factors must be controlled as well: lipids, blood pressure, BMI, smoking, physical fitness with life-style modifications as well as drugs. I would be reluctant to prescribe aspirin to a patient with uncontrolled BP. I believe that aspirin is much less important in primary prevention than control of these risk factors.

I believe that individuals who have never experienced a vascular event may be at almost as great a risk of an event as those who have experienced an event, especially if treatment has reduced risk factors in the latter group.

The Current Evidence Is Insufficient To Rule Out A Small Yet Important Benefit

5-4 ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE: A Meta-analysis of Randomized Trials

The effect of long-term, low dose aspirin on patients with peripheral artery disease (PAD) is uncertain.

Despite the paucity of data, major guidelines support the use of aspirin as first-line therapy for patients with PAD. However, the FDA concluded that there is insufficient evidence to support a labeling indication for aspirin in patients with PAD.

This meta-analysis of patients with PAD evaluated all the available evidence from prospective, randomized trials of aspirin alone or in combination with other antiplatelet drugs in secondary prevention of cardiovascular events. It tested the null hypothesis that aspirin was not different from placebo in reducing risk of the combined primary endpoint of non-fatal MI, non-fatal stroke, and cardiovascular death.
A literature search found 18 prospective, randomized trials of aspirin, with or without dipyridamole (5269 individuals with PAD). Aspirin dose ranged from 100 mg/d to 1500 mg/d for monotherapy, and from 25 mg aspirin + 75 mg dipyridamole to 325 mg aspirin + 75 mg dipyridamole.

Primary endpoint = cardiovascular events (non-fatal MI, non-fatal stroke, and cardiovascular death).

A total of 251 cardiovascular events (the primary endpoint) took place among 2823 patients receiving any aspirin vs 269 among 2446 controls (8.9% vs 11%; 12% reduction). The difference was not statistically significant.

The risk of non-fatal stroke was lower in the aspirin group (1.8% vs 3.1%). This was statistically significant.

Effect of aspirin monotherapy on the primary outcome: 125 cardiovascular events among 1516 patients vs 144 events among 1516 controls (8.2% vs 9.6%; not significant ). Aspirin was associated with a significant reduction in non-fatal stroke (2.1% vs 3.4%).

Two trials compared low dose (100 mg) aspirin monotherapy with placebo: 112 cardiovascular events occurred among 823 participants vs 127 events among 819 placebo participants (13.6% vs 15.5%). Although not statistically significant, the population studied was small, and the 95% confidence interval was wide, potentially limiting detection of important cardioprotective events.

“Results of this meta-analysis demonstrated that, for patients with PAD, aspirin therapy alone or in combination with dipyridamole did not significantly decrease the primary endpoint of cardiovascular events.” This may reflect limited statistical power. Smaller levels of benefit, such as a 20% reduction, cannot be excluded with the available evidence.

Aspirin was associated with a significant reduction of non-fatal stroke.

There was no significant benefit noted for non-fatal MI, cardiovascular mortality or all-cause mortality.

Conclusion: This meta-analysis did not demonstrate a significant benefit of aspirin vs placebo on cardiovascular events in patients with PAD. Aspirin significantly reduced risk of non-fatal stroke.

The current evidence is insufficient to rule out a small yet important benefit.

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The NNT with aspirin for one year to benefit one patient could not be calculated from the data in the meta-analysis. It is likely to be very large.

If atherosclerosis is widespread and severe, it may be too much to ask aspirin to benefit. The subjects in this meta-analysis had advanced PAD.

Aspirin is still being highly advertised for primary prevention.
Guidelines continue to recommend aspirin. Many PCPs will continue to use it for primary and secondary prevention.

Diabetes with or without PAD is considered an indication for aspirin prophylaxis.

The significant reduction in non-fatal stroke may be enough to convince some patients to accept aspirin prophylaxis.

How should primary care clinicians now respond to this latest information?

1. Aspirin is effective in secondary prevention. It may be effective in primary prevention.
2. If aspirin is used, low doses should be prescribed (75-81 mg/d). Low doses are effective and cause less harm.
3. Patients should be made aware of the possible harm of bleeding as well as possible benefits in order to make a personal informed choice for primary prevention. Harms and benefits are roughly equal. Patients may fear the harm of bleeding less than the harm of stroke and MI.
4. Aspirin prophylaxis probably does lower risk of cardiovascular complications. Aspirin cannot approach the effectiveness of controlling other well established risk factors (lipids, BMI, blood pressure, fitness, smoking) in lowering risk.

ASTHMA

*Combined Agents Are Clearly The Wiser Choice*

1-5  **FDA PANEL ADVISES BANNING 2 POPULAR ASTHMA DRUGS**

The panel, which advises the FDA on safety issues, recommends that the FDA ban marketing of 2 popular drugs—the long acting beta-agonists formoterol and salmeterol. These inhaled drugs, when used alone, are associated with increased risk of rare, but serious, adverse effects—in some cases death.

The committee advises banning the drugs when used alone—not when combined with a corticosteroid.

NIH guidelines recommend asthma patients first receive low-dose inhaled corticosteroid. Then, if symptoms remain uncontrolled, they could receive additional medications.

“Our recommendation is that the combined agent is clearly the wiser choice.”

The FDA typically follows the panel’s recommendations.

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*The FDA may or may not follow the advice of the panel.*

*Formoterol and salmeterol already have black box warnings. This article emphasizes caution for primary care.*
ATRIAL FIBRILLATION

5-2 EFFECT OF CLOPIDOGREL ADDED TO ASPIRIN IN PATIENTS WITH ATRIAL FIBRILLATION  [See ASPIRIN]

BODY-MASS INDEX

Mortality Was Lowest At BMI Of 22.5 To 25.

3-1 BODY-MASS INDEX AND CAUSE-SPECIFIC MORTALITY IN 900 000 ADULTS

A Collaborative Analysis of 57 Prospective Studies.

This study analyzed baseline BMI vs mortality in over 890 000 participants. (At baseline, 61% male; mean age 46; range 35-89; mean BMI 25). None had a history of heart disease or stroke.

The analyses were adjusted for age, sex, and smoking. Omitted the first 5 years of follow-up, leaving over 66 500 deaths of known cause during a mean of 8 years following the omitted 5 years.

In both sexes mortality was lowest at BMI of 22.5 to 25.

Mortality increased for each 5 kg/m2 increase in BMI: Overall mortality 40%; Ischemic heart disease 40%; Stroke 40%; Neoplastic disease 10%; Respiratory disease (chiefly COPD) 20%.

In the upper range (BMI 25-40) BMI was also strongly and positively associated with mortality due to diabetes, non-neoplastic kidney disease, and non-neoplastic liver disease (chiefly cirrhosis).

Absolute excess mortality in males each year:

For those with a BMI 35-40 (vs 22.5-25) excess mortality was about 5 per 1000

For those with a BMI 40 and above, excess mortality was about 13 per 1000

In the present decade, about 29% of vascular deaths and 8% of neoplastic deaths in late middle-age could be attributable to having a BMI greater than 25.

Median survival at age 60:

For people who reach a BMI of 25-27, life was shortened by 0-1 years

For BMI 28-30, by 1-2 years

For BMI 30-35, by 2-4 years

For BMI 40-45, by 8-10 years.

Below 22.5 mortality rose as BMI fell. (Inverse relationship) The inverse relationship was mainly because of respiratory disease and lung cancer. It was much stronger for smokers than for non-smokers.

Much of the mortality risk in the low BMI subjects could be non-causal (ie, not due to low BMI per se, but to the cause of the low BMI). If so, the real optimum BMI might be somewhat lower than 22.5 to 25.
Association of other risk factors with increasing BMI: BP; Lipids; Diabetes; Smoking:
The absolute excess risks for higher BMI and smoking were roughly additive.
Although both smokers and non-smokers follow the same BMI mortality trajectory, the
difference in mortality between the two is striking. In those with a BMI 22.5 – 25, yearly all-
cause mortality per 1000 was about 8 in non-smokers, and 15 in smokers.
Smoking can cause weight loss. Thus there would be substantially more smokers in the lower
BMI categories.
Effective interventions for weight loss lower BP, favorably affect lipoprotein particles, and increase
insulin sensitivity. “At least some of the major aspects of obesity are therefore reversible.”
In adult life, it may be easier to avoid substantial weight gain than to lose that weight once it has
been gained. By avoiding a further increase in BMI from 28 to 32, a typical person in early middle-age
would gain about 2 years of life expectancy. By avoiding an increase from 24 to 32, a young adult
would on average gain about 3 extra years of life.
Conclusion: BMI is a strong predictor of overall mortality, both above and below BMI of 22.5 -25
(the apparent optimum). The excess of mortality below 22.5 is due mainly to smoking.

This remarkable study should be required reading for all primary care physicians and patients.
Smoking + obesity is a deadly combination.
It is easier to calculate BMI than measure waist and hip circumference and calculate the ratio.
The article is long and complex. It was difficult to abstract.
Read the full abstract.

BONE MINERAL DENSITY

“Is Potentially Misleading and A Misuse Of Healthcare Resources”

6-4 MONITORING BONE MINERAL DENSITY DURING ANTiresorptive Treatment
FOR OSTEOPOROSIS

Antiresorptive treatment for osteoporosis is usually prescribed for 5 years. It reduces the risk of
fractures. It causes adverse effects. Patients and their doctors seek reassurance that the treatment is
working.

The most common way to monitor response is repeated measurement of bone mineral density
(BMD) using dual energy X-ray absorptiometry (DXA), an approach endorsed by guidelines.
A study in this issue of BMJ analyzed the effects of alendronate vs placebo in over 6000 women
with low BMD. BMD at hip and spine was measured at 4 time points (before treatment, one, two and
three years). Treatment was estimated to be beneficial in the vast majority of women. Overall, in 3 years, the mean increase in hip BMD was 0.030 g/cm$^3$. At 3 years, the 95% distribution for the actual overall effects did not overlap zero, ranging from an increase of 0.019 to 0.041 g/cm$^3$.

However, measurements in individuals (within a person) varied considerably more, often showing apparent decreases in BMD. The apparent 95% distribution of change after 3 years ranged from a decrease of 0.031 to an increase of 0.075 g/cm$^3$.

The large within-person variation in BMD is likely to be an understatement, as BMD measurements in practice have considerably more within-person variation than measurements in clinical trials.

To detect significant changes in BMD, the rate of bone gain must be larger than the precision error of DXA measurement. Although gain may be achieved after 5 years of bisphosphonate therapy, the changes in BMD within 1 or 2 years is generally too small to be detected. Even changes of 7% or more may not be reliably shown in individual patients. Not being able to detect a change until 5 years is clearly not clinically useful.

The large variability associated with measurement of BMD in an individual obscures the treatment response. This makes monitoring unnecessary and potentially misleading.

A final nail in the coffin for monitoring BMD is the observation that only a small proportion of reduction in fractures attributable to alendronate is explained by a change in BMD. Only 16% of the decrease in risk of fracture is attributable to an increase in BMD. Some studies have found reductions in fracture regardless of whether BMD is increased or decreased on treatment.

“The clear implication for clinical practice is that patients may be given inappropriate advice if changes in bone mineral density are used to monitor treatment.”

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*The national effort to reform medical insurance calls for studies to determine the most cost-efficient diagnostic tests. Testing is overdone. The use of DXA may be a good example.*

**CARDIOVASCULAR DISEASE**

*A Higher Sodium/Potassium Excretion Ratio Was Associated With Increased Risk Of CVD.*

**1-1 Joint Effects of Sodium and Potassium Intake on Subsequent Cardiovascular Disease: The Trials of Hypertension Prevention Follow-up Study (TOHP)**

Lower levels of sodium intake and higher levels of potassium intake are associated with reduced risk of hypertension. Long-term interventions aimed at sodium reduction and potassium substitution may lead to a reduced risk of CVD.
This follow-up study was based on intermittent measurements of 24-hour urinary electrolyte excretion. It assessed the relation of 24-h urinary excretion of sodium and potassium and their ratio with subsequent CVD (stroke, myocardial infarction, coronary revascularization, or CVD mortality) through 10 to 15 years of post trial follow-up.

Excretion of sodium increased with increasing BMI, for potassium excretion, there was a statistically significant inverse trend across quartiles, with a 45% reduction in risk of CVD among participants in the highest quartile vs the lowest quartile.

For the sodium to potassium ratio, the trend across quartiles was statistically significant:

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Na/K Excretion Ratio</th>
<th>Relative Risk of CVD</th>
<th>Cardiovascular Events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;2.2</td>
<td>1.00</td>
<td>7.7</td>
</tr>
<tr>
<td>2</td>
<td>&gt;3.4</td>
<td>1.06</td>
<td>7.4</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>1.35</td>
<td>8.4</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>1.77</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Absolute difference Q4 – Q1 = 2.4%; NNT = 41 (My calculations RTI)

The sodium to potassium excretion ratio displayed the strongest association with risk of CVD. For each unit of increase in the ratio, there was a 24% increase in risk of CHD and stroke.

Conclusion: The totality of evidence suggests that lowering dietary sodium intake, while increasing potassium consumption at the population level might reduce incidence of CVD.

Of interest—sodium intake increased as BMI increased.

See Practical Pointers May 2007 [5-1] for an excellent discussion of sodium and potassium in the pathogenesis of hypertension abstracted from NEJM May 10, 2007; 359: 1966-78. It stresses the need for a higher potassium intake as well as a lower sodium intake.

I believe control of potassium and sodium intake is essential for a reduction in population prevalence of hypertension and CVD. On a population basis, this intervention could have a beneficial effect matching any other intervention.

The Gap Between The Standards Set In CVD Prevention Guidelines And Clinical Practice Continues.

3-2 CARDIOVASCULAR PREVENTION GUIDELINES IN DAILY PRACTICE

Guidelines in Europe give high priority to prevention of CVD in clinical practice. Lifestyle preventive measures include: stopping smoking; making healthy food choices; and becoming physically active.
The evidence for CVD prevention and rehabilitation programs that address lifestyles is compelling. Yet access to such programs in Europe is limited.

This article describes three cross sectional surveys in 8 European countries 1997-2007. It asked whether preventive lifestyle measures had improved over the years, and whether the recommendations were followed in practice.

All three surveys identified consecutive hospitalized patients (men and women; mean age 60). All had a recent occurrence of acute CVD. All were interviewed one year later to determine if lifestyle preventive measures had been implemented over time.

Results (total of 8 countries):

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>20</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Overweight and obesity</td>
<td>77</td>
<td>80</td>
<td>83</td>
</tr>
<tr>
<td>Obesity</td>
<td>25</td>
<td>33</td>
<td>38</td>
</tr>
<tr>
<td>Raised BP</td>
<td>58</td>
<td>58</td>
<td>61</td>
</tr>
<tr>
<td>Raised cholesterol</td>
<td>94</td>
<td>77</td>
<td>46</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13</td>
<td>20</td>
<td>28</td>
</tr>
</tbody>
</table>

The results should be a cause for concern to all health policy makers, physicians, and other health-care professionals.

Unhealthy lifestyles draw attention to the need for a social strategy for CVD prevention.

It is difficult for patients to change behavior despite the development to a life-threatening disease. Sustained professional support is required to encourage lifestyle change. Drug treatment is not enough.

European health-care systems are dominated by acute care, medical technology, devices, and pharmacological treatment. All patients with CVD would benefit from access to comprehensive cardiovascular prevention and rehabilitation programs. To salvage the acutely ischemic myocardium without addressing the underlying lifestyle causes is futile. “We need to invest in prevention.”

This is discouraging. If people with a life-threatening wake-up call do not or cannot change lifestyles, how can we expect those with no history of CVD to improve their lifestyles?

Physicians must remain dedicated to education of their patients and to relentless promotion of healthy lifestyles in the general population.

An important step: Physicians must act as role models. “Physician, heal thyself!”
Social interventions have begun. New York City has taken steps to limit trans fats and salt consumption, and encouraging publication of caloric content of foods in restaurants. Schools are limiting access to soft drinks and encouraging healthy foods in cafeterias.

Nutrition facts published on food packaging are helpful. People should be encouraged to read and understand them.

Change will not be easy. It will be slow. I have hopes.

“Aspirin Continues To Be Underused”

3-3 ASPIRIN FOR PREVENTION AND TREATMENT OF CARDIOVASCULAR DISEASE

[See ASPIRIN]

A New Approach To Treatment Of Blood Pressure?

5-1 USE OF BLOOD PRESSURE LOWERING DRUGS IN THE PREVENTION OF CARDIOVASCULAR DISEASE: A Meta-Analysis Of 147 Randomised Trials In The Context Of Expectations From Prospective Epidemiological Studies. [See HYPERTENSION]

CARDIOVASCULAR RISK ASSESSMENT

“Ancillary Testing Adds Little To The Prediction Of Individual Cardiovascular Risk. It Does Not Affect Care, Lifestyle, Adherence, or Clinical Outcomes”

1-2 EVALUATING CARDIOVASCULAR RISK ASSESSMENT FOR ASYMPTOMATIC PEOPLE

Formal risk prediction tools increase accuracy of clinical assessment of future risk of cardiovascular disease in asymptomatic patients. Prediction tools that are easy to use and that integrate the Framingham criteria into one global risk score have evolved to aid risk assessment.

New putative clinical risk factors have been described: Chronic kidney disease, metabolic syndrome, and numerous laboratory markers.

Do ancillary tests in asymptomatic patients improve accuracy of predicting cardiovascular risk? What effect might they have on patient care, behavior, and clinical outcomes?

Indiscriminant testing of asymptomatic patients could waste resources, increase anxiety, and lead to interventions that have not been proved.

A positive or abnormal value for a new risk factor will be more useful if:

- The more abnormal the test, the greater the risk of an event.
• The strong association persists after the contribution of traditional risk factors has been taken into account.
• The test discriminates well between individuals who have an event in the future and those who will not.
• The testing method is reliable and standardized.
• The test value leads to a change in risk estimates, which are large enough to justify altering the intended management.
• Results of clinical trials predict that the altered management plan will improve outcomes.

The article considers laboratory tests; coronary artery imaging (both for carotid calcification and obstructive disease); carotid and peripheral artery screening; metabolic syndrome; resting and exercise EKG.

Implications for clinical practice:
According to the available evidence, ancillary testing in most asymptomatic patients adds little to the prediction of individual cardiovascular risk. It does not affect care, lifestyle, adherence, or clinical outcome.

Ancillary testing in most middle age people is premature and potentially wasteful of resources. An alternative strategy, which needs to be studied, is to ensure that all adult patients (and their doctors) are aware of their cardiovascular risk by using simple, accessible clinical risk calculators, and adopt a management plan appropriate to their level of risk.

“No randomized evidence to date has shown that informing clinicians and patients of the absolute risk of cardiovascular events leads to changes in care or improvement in outcomes.”

In primary care, we have little use for additional risk markers. Our problem is to apply the ones we already have.

CARING FOR THE PATIENT

“For The Secret Of The Care Of The Patient Is In Caring For The Patient.”

4-1 TOWARD A RESTORATIVE MEDICINE—THE SCIENCE OF CARE

The good physician knows his patients through and through. Time, sympathy and understanding must be lavishly dispensed. The reward is to be found in that personal bond which forms the greatest satisfaction of the practice of medicine. One of the essential qualities of the clinician is interest in humanity. “For the secret of the care of the patient is in caring for the patient.” (“The Care of the
Peabody added: “The clinical picture is not just a photograph of a man sick in bed, it is an impressionistic painting of the patient surrounded by his home, his work, his relations, his friends, his joys, sorrows, hopes, and fears.”

Many at that time believed that the key to personal medical care was the home visit. These visits allow physicians to learn about the life circumstances of their patients, including financial anxiety, and domestic incompatibility, and about their own (the physician’s) personal qualities such as self-centeredness, altruism, and gentleness.

In 1977, a half century after Peabody, a new medical model was proposed that essentially incorporated Peabody’s approach. A bio-psycho-social approach was proposed, with a central focus on the person. This placed the patient’s narrative at the center of the clinical evaluation.

The patient-centered approach to patient care is crucial for high-quality care. How the interview is conducted matters. An open-ended narrative interview allows the patient to become personally engaged with the interviewer, facilitates rapport, elicits individual attitudes and feelings, and clarifies the meaning of illness to the patient. An effective clinical encounter should elicit attitudes and feelings as well as facts.

An essential quality of a clinician is an interest in humanity. Such interest is no less apparent in physicians today than it was in Peabody’s time.

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Please read the entire abstract. Times have changed—some for the better, some for the worse.

Young physicians rightly focus their attention on application of the “scientific” medicine learned in medical school. They focus on not missing a critical diagnosis. And applying the correct treatment for the physical disease.

Wisdom comes with age. It takes time to develop an ongoing empathetic relationship with patient and family—a luxury not often afforded to medical specialists. Primary care clinicians have a great advantage in this respect. Specialists are just as empathetic as primary care clinicians, but they focus more on the organ. And they do it with exceptional skill. The time for emotional connectedness with patient and family is limited.

The article mentions home visits. They were part of general practice when I started. There is some interest in reviving home visits as part of the remit of the “medical home”.

I remember, when I was a child, the frequent home visits of “our doctor”. He became part of the family. He would always sit down and chat. He was my role-model.
CELIAC DISEASE

Should Primary Care Physicians Test Patients With IBS For CD?

YIELD OF DIAGNOSTIC TESTS FOR CELIAC DISEASE IN INDIVIDUALS WITH SYMPTOMS SUGGESTIVE OF IRRITABLE BOWEL DISEASE

In community surveys, the prevalence of irritable bowel syndrome (IBS) varies between 5% and 20% depending on the criteria used for diagnosis.

Prevalence of celiac disease (CD) in the U.S. is almost 1%.

IBS and CD are prevalent conditions that share a common set of symptoms.

Guidelines in the U.K. recommend routine exclusion of CD in all patients with symptoms of IBS.

This systematic review and meta-analysis estimated the prevalence of CD in adults who met the diagnostic criteria for IBS.

Case series and case-control studies that used serological tests for CD were eligible for inclusion. Serological tests for CD included: IgA-class A antigliadin antibody (AGA); endomysial antibody (EMA); and tissue transglutaminase antibody (tTGA).

Yield of IgA-class AGA-testing in individuals meeting diagnostic criteria for IBS:

Seven studies reported data in 1104 subjects with IBS. Pooled prevalence of persons who met diagnostic criteria for IBS who tested positive for AGA = 4%.

Five studies offered duodenal biopsy to individuals who tested positive for AGA.

Biopsy was consistent with CD in only 8 of 27 individuals with positive AGA.

Yield of EMA or tTGA-testing in individuals meeting diagnostic criteria for IBS:

Thirteen studies used either test in 2021 individuals; 41 (2%) tested positive.

Five studies (n = 1147) provide data on duodenal biopsy in those testing positive; 33 of 36 had histological changes consistent with CD. Thus, 33 of 1147 (2.9%) individuals in 5 studies had biopsy-confirmed CD.

Odds ratio in case-control studies:

Five case-control studies followed 1) Cases (n = 952) who met diagnostic criteria for IBS vs 2) Controls (n = 1798; no IBS). All received biopsy. 34 cases (3.6%) had biopsy proved CD vs 12 controls (0.7%). Odds ratio = 4.34. Again no significant difference between types of IBS.

In persons meeting diagnostic criteria for IBS, the prevalence of positive serological tests for CD was about 3%. The prevalence of biopsy-proved CD was about 3% in those with positive diagnostic tests for CD.

The prevalence of biopsy-proved CD was similar between subtypes of IBS (diarrhea predominant, constipation predominant, and mixed).
Conclusion: The prevalence of CD in patients meeting diagnostic criteria of IBS is in the region of 3%, EM antibody and tTG antibody testing should be the preferred serological tests.

Primary care physicians who encounter patients with symptoms of IBS should consider screening for CD.

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The investigators found that constipation-predominant IBS was just as likely to be related to CD as diarrhea-related IBS. This surprised me.

Clinicians may be more likely to screen for conditions that have a major and immediate effect on health (eg, breast cancer, prostate cancer and CVD) than for conditions that have minor and less immediate effects. Just as gamblers in Las Vegas may be more likely to play a slot machine that has a big jackpot.

CLOPIDOGREL

5-2 EFFECT OF CLOPIDOGREL ADDED TO ASPIRIN IN PATIENTS WITH ATRIAL FIBRILLATION [See ASPIRIN]

CO-PAYMENTS AND THE INITIATION OF DRUG THERAPY

When Co-Payments Are Increased, Initiation Of Therapy Is Delayed

4-2 COST SHARING (CO-PAYMENTS) AND THE INITIATION OF DRUG THERAPY FOR THE CHRONICALLY ILL

Health care plans have responded to rising prescription costs by restricting payments. This has resulted in increased co-payments for drugs by policy-holders.

This study examined whether increasing co-payments (cost-sharing by patients) affects the initiation of drug treatment.

Identified patients with newly diagnosed hypertension, hypercholesterolemia, and diabetes. (n = over 17 000). Identified disease-specific prescribed medications. The majority of patients received multiple prescriptions.

Primary outcome = the time until initiation of the prescription drug therapy, defined as the number of days between a patient’s first diagnosis and the time of filling of the first disease-specific prescription.

When co-payments were doubled, the % of patients with newly-diagnosed hypertension,
who initiated therapy at one year after the increase, fell from 55% to 40%. Compliance also fell for patients receiving prescriptions for hypercholesterolemia and diabetes.

The effect of doubling co-payments depended on the patient’s history of prescription drug use. Compared with patients with no drug use in the year prior to the index date, patients with any drug use in that period initiated therapy earlier, and were much less sensitive to price.

Chronically ill patients are sensitive to the cost of prescription drugs. Out-of-pocket costs prevent patients from promptly initiating medically necessary care.

The % of newly diagnosed patients who had not initiated a drug to treat hypertension, hypercholesterolemia, and diabetes by 5 years was 21%, 36% and 33%.

Conclusion: High cost-sharing delays the initiation of drug therapy for patients with newly diagnosed chronic diseases.

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During my years of practice, I assumed that patients were taking their medications.

I frequently asked patients to bag all their medication for review at the office visit. Many did not respond to this request. I could not understand why. Perhaps because they did not have the prescription filled or were not taking it regularly.

Prescribing multiple drugs undoubtedly lowers compliance.

Cost is an important factor in the benefit/harm-cost ratio of medications.

The recent willingness of several major pharmacies to offer generics at $4 for one-month’s supply or $10 for 3 month’s supply is most welcome. This should increase compliance. Since all doses of drugs cost the same, use of a pill cutter will further decrease cost.

The most empathetic physician guided by the best of evidence-based practice will not benefit a patient who cannot afford the medications prescribed.

CORONARY HEART DISEASE

Provides Some Guidance To Primary Care Clinicians

6-6 THERAPIES FOR TYPE 2 DIABETES AND (STABLE) CORONARY HEART DISEASE: A Randomized Trial [See DIABETES]
DIABETES

This 6-Year Trial Reports No Benefits From Intensive Control

1-8 GLUCOSE CONTROL AND VASCULAR COMPLICATIONS IN VETERANS WITH TYPE-2 DIABETES

The effects of intensive glucose control on cardiovascular (CV) events in patients with long-standing type-2 diabetes (DM-2) remain uncertain. Two recent large studies of intensive control reported no significant decrease in cardiovascular events.

This VA study compared the effects of intensive control vs standard glucose control on CV events. It randomized 1791 military veterans with DM-2 (mean age 60; 40% with previous CV disease) to 1) Intensive control, or 2) Standard control. Follow-up = 6 years.

The goal was an absolute HbA1c reduction of 1.5% in the intensive group as compared with the control group.

At 6 months, mean HbA1c decreased to 8.4% in the standard group, and to 6.9% in the intensive group, and remained at these levels throughout 6 years. The prespecified goal of an absolute difference of 1.5% between groups was met.

At 6 years, the observed CV event rate was 33.5% in the standard group and 29.5% in the intensive group—a relative reduction of 12% (Hazard ratio = 0.88; CI = 0.74 to 1.05)

No significant differences between groups in time to death from CV disease.

“For now, appropriate management of hypertension, dyslipidemia, and other cardiovascular risk factors appears to be the most effective approach to prevention of cardiovascular morbidity and mortality.”

Conclusion: Over 6 years, intensive glucose control did not significantly reduce cardiovascular events in patients with previously diagnosed type-2 diabetes.

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I would agree that lipid, weight, and BP control are the most effective approaches to reducing cardiovascular events in patients with DM-2, as well as in those without.

I would not agree that glucose control lacks benefit on long-term reduction of cardiovascular events:

1) Six years of intensive control is insufficient time to judge benefits. Beginning better control at an earlier age and continuing for many years may lower CV complications. The classical link between DM-2 and peripheral atherosclerosis may take many years to develop.

2) Note that the observed event rate in the intensive group was 12% lower than in the standard
group (confidence interval 0.74 to 1.05). Although this did not reach the standard criterion for statistical significance, a longer period of intensive control may have resulted in statistical significance.

3) The subjects had a high rate of established CV disease. They were at high risk. If intensive therapy was started before this risk was established, and continued for a longer time, the benefit may have been greater. Intensive control in patients with established CV disease may not be as beneficial as beginning control before CV is established.

4) Good control lessens microvascular complications. The study showed no benefit in reducing microvascular complications except for albuminuria. This, again, may have been due to insufficient time to observe a benefit.

5) Do these studies negate the classical link between diabetes and peripheral arteriosclerosis? I believe not.

6) DM-2 has for many years been considered a risk factor for CHD, equal to that of established CHD. Do these studies negate the classical link between diabetes and cardiovascular disease? I believe not.

7) Rosiglitazone, one of the drugs used in the trial, in retrospect, may have been a poor therapeutic choice.

Intensive control, especially with insulin, leads to frequent hypoglycemia, weight gain, and probably an increase in death, especially in the elderly. We should be cautious in attempting intensive control in the elderly—not lowering HbA1c below 7%.

**Glucose Control Is Still Beneficial Long-term**

4-5 **GLUCOSE CONTROL IN TYPE-2 DIABETES: Still Worthwhile And Worth Pursuing**

Two large studies in the 1990s demonstrated benefit of improved glucose control on micro-vascular complications (eyes, kidneys, and nerves).

The DCCT in patients with type-1 diabetes provided evidence that intensive glucose control led to approximately 60% reduction in the risk of progression of micro-vascular complications.

The UKPDS, in patients with type-2 diabetes, showed that 10 years of improved glycemic control resulted in a 25% reduction in micro-vascular complications.

Following publication of these studies, the benefit of improved glucose control in micro-vascular complications was no longer debated.
In 2008-09, three long-term clinical studies of glucose control and macro-vascular complications in type-2 diabetes were reported. They provided conflicting evidence of benefits of intensive control on macro-vascular complications.

ACCORD involved over 10 000 patients with a history of cardiovascular events or at increased risk. The study was stopped at 3.5 years because of an unexpected 22% increase in all-cause mortality in the intensively treated group.

VADT was similar to ACCORD, but included more cardiovascular events in the composite endpoints. Intensive control was associated with more hypoglycemia. There was no difference between treated and control groups in mortality or the composite primary outcome. A severe episode of hypoglycemia strongly predicted mortality.

ADVANCE enrolled over 11 000 high-risk patients who had known cardiovascular disease, or at least one risk factor. Intensive glucose control was not effective in reducing macro-vascular outcomes, but did not increase cardiovascular or all-cause mortality.

In sum, the trials suggest that a possible benefit on cardiovascular outcomes may be observed in patients with a shorter duration of diabetes, better glucose control, younger age, no previous cardiovascular disease, or fewer risk factors at the time of initiation intensive control.

Long-term follow-ups of the DCCT and UKPDS suggest that prior intensive glucose control may have beneficial effects lasting beyond the period of improved control. The DCCT patients were followed up for 11 years after the period of intensive control. During this period, glucose control was similar in the prior intensive group and the control group. In the intensive group, seventeen years after beginning the trial, there was a 42% reduction in risk of any cardiovascular event and a 57% reduction in non-fatal MI, non-fatal stroke, or cardiovascular death.

Ten years after completion of the intervention phase of the UKPDS, glucose control no longer differed between groups, yet patients in the intensive-control group benefited. Differences in micro-vascular complications were maintained, and risk of MI was reduced by 15%, and all-cause mortality by 13%.

The mechanisms for this “legacy effect” are not known.

It seems reasonable to set the appropriate goal of HbA1c at less than 7% in younger patients. They are likely to have a shorter duration of diabetes, fewer risk factors, and no history of prior cardiovascular disease. They can sense hypoglycemia. A more liberal target of less than 7.5% would seem appropriate for older patients who have advanced diabetes-related complications, or who experience severe hypoglycemia.
This study is a good example of a mistake we may make when we transfer results of trials with limited applicability (older patients with long-standing diabetes, a history of cardiovascular disease, and risk factors other than diabetes itself) to the population of younger patients (with short duration of diabetes, no history of cardiovascular disease and fewer risk factors).

The ADA Will Likely Soon Propose Using Hba1c As A Diagnostic Test

**4-8 HEMOGLOBIN A1c POISED TO BECOME PREFERRED TEST FOR DIAGNOSING DIABETES**

HbA1c appears to be on the threshold of official recognition as the preferred diagnostic test for diabetes.

A consensus statement was issued in 2008 calling for adoption of HbA1c as a screening and diagnostic test.

The (arbitrary) cut-off point for diagnosis will probably remain in debate. A level of 6% or less has been defined by some authorities as normal; 6.1% to 6.9% as pre-diabetes; and 7.0% or greater as diabetes.

The test is looked upon more favorably than in 2003 (the last ADA recommendation) because the test is now more standardized. As of September 2007, certification from the National Glyco-hemoglobin Standardization Program required manufacturers to produce tests that result in readings that are within + or – 0.85% of true HbA1c levels from 4% and 12%.

The HbA1c test is easy to use. It should facilitate diagnosis earlier in the disease, when interventions are most successful.

“Probably more than 40% of people with diabetes are undiagnosed, and one reason might be that the test used most to diagnose diabetes requires fasting.”

---------

I agree that more patients would be screened if Hba1c were used.

A range of + or – 0.8% may lead to false positive and false negative results. Patients with Hba1c in the 6% to 7% range may require confirmation with a plasma glucose test.

The aim of diagnosis and treatment of diabetes is to reduce rate of macro-and micro-vascular complications. Complications of diabetes are much less likely at 6% or lower.

Each Low Risk Lifestyle Risk Factor Was Independently Associated With A Lower Incidence

**6-3 LIFESTYLE RISK FACTORS AND NEW-ONSET DIABETES MELLITUS IN OLDER ADULTS**
This study determined how lifestyle factors, assessed later in life, relate to new-onset type-2 diabetes (DM-2) in a broad and relatively unselected population of older adults.

Prospectively examined associations of lifestyle factors with incident DM-2 during a 10-year period among over 4800 randomly selected men and women age 65 and over (mean = 73)

Low-risk lifestyle groups were defined by:
1) Physical activity level (leisure-time activity and walking pace) above the median
2) Dietary score in the top 2 quintiles (higher fiber intake and higher polyunsaturated fat to saturated fat ratio, lower trans fat intake, and lower mean glycemic index)
3) Never smoked or former smoker over 20 years ago
4) Alcohol use (light or moderate)
5) Body mass index less than 25
6) Waist circumference of 88 cm for women and 92 cm for men, or under

Main outcome measure = incident DM-2 defined by new use of insulin or oral hypoglycemic drugs.

During 10 years, 337 new cases of DM-2 occurred (10 per 1000 person-years).

Each low risk lifestyle risk factor was independently associated with a lower incidence of DM-2.

Nine of 10 cases of DM-2 in this older population appeared attributable to the 6 risk factors. If these factors are causal, 9 of 10 cases of DM-2 might have been prevented.

Conclusion: Even later in life, combined favorable lifestyle factors are associated with a markedly lower incidence of new-onset diabetes.

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Diabetes not uncommonly begins in older age. Over 10 years, an estimated 10 in 1000 persons (one in every 100) over age 65 would develop new-onset DM-2. On a population basis, this would be a high number. Costs of treatment would be high. I believe many cases could be avoided.

Of course, the risk factors pertain to younger persons as well.

The goal is to go into old age with no risk factors. And to remove those that do exist at the time.

I believe the greatest challenge and the most productive intervention of our new national health care plan is to encourage and monitor adoption of healthy lifestyles. The only means to accomplish this lies in long-term continuous primary care—a “Medical Home”.

The study strengthens the association of benefit of low-to-moderate alcohol intake. Abstinence has been termed a risk factor for years.
What is the optimal treatment for patients with type-2 diabetes (DM-2) and angiographically defined, stable coronary heart disease (CHD) ?

This randomized trial entered and followed 2368 patients with both DM-2 and CHD. All had CHD documented on angiography. Ischemia was symptomatic in 82% of patients. All patients were treated according to current guidelines to target levels of HbA1c less than 7%, LDL-cholesterol less than 100mg /dL, and BP of 130/ 80 or less. Medications included statins, aspirin, beta-blockers, and either ACE inhibitors or angiotensin II blockers.

All received counseling regarding smoking, weight loss, and exercise.

Randomized to:

A. 1) A group pre-selected for CABG (n = 763), or 2) A group pre-selected for PCI (n =1605)

(Selection was by the responsible physician as the most appropriate therapy for each patient.)

B. Both groups were then divided into subsets:

<table>
<thead>
<tr>
<th>CABG stratum</th>
<th>PCI stratum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-selected for CABG (n = 763)</td>
<td>Pre-selected for PCI (n = 1605)</td>
</tr>
<tr>
<td>Randomized to IMT-alone (n = 385)</td>
<td>Randomized to prompt PCI + IMT (n = 798)</td>
</tr>
<tr>
<td>Randomized to prompt CABG + IMT (n = 378)</td>
<td>Randomized to IMT-alone (n = 807)</td>
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</tbody>
</table>

(Thus, all 2368 patients received IMT. Patients in the CABG stratum had significantly more coronary disease.)

(Patients in the CABG group assigned to IMT-alone were to undergo revascularization with CABG during follow-up only if clinically indicated. Patients in the PCI group assigned to IMT-alone were to undergo revascularization with PCI during follow-up only if clinically indicated.)

C. All subjects were also randomized to: 1) Insulin provision (insulin and/or sulfonylurea), or

2) Insulin sensitization (metformin and/or thiazolidinedione)

Primary endpoint = death from any cause. Secondary endpoint = composite of death, non-fatal MI, and stroke (major CV events).

All patients assigned to IMT-alone underwent careful monitoring, and 42% had changes in the clinical course during 5-years of follow-up that called for later revascularization. At 3 years, 43% of patients in the insulin-sensitization group and 12% of those in the insulin-provision group received medications from the alternative drug class. (Ie, considerable cross-over between groups)

In the insulin-sensitization group, compared with the insulin provision group, mean HbA1c levels
were significantly lower, the BMI significantly lower, plasma insulin levels consistently lower, and there were fewer episodes of severe hypoglycemia, less weight gain, and higher HDL-cholesterol levels.

Overall, the rate of death from any cause did not differ significantly between the various groups; 88% survived at 5-years. The rate of freedom from major CV events did not differ significantly between the revascularization groups and the IMT-alone groups, or between the insulin-provision and the insulin-sensitization groups.

However, at 5 years, patients in the CABG stratum who were pre-assigned to prompt surgery had significantly fewer major CV events (especially non-fatal MI) than those in the CABG stratum assigned to the IMT-alone group (22% vs 30%). In contrast, rates of CV events among patients in the PCI stratum who were assigned to prompt PCI did not differ significantly from those in the IMT-alone group.

Severe hypoglycemia was more frequent in the insulin-provision group (9%) The fact that the majority of patients in the IMT-alone groups did not require revascularization during 5-years suggests that many may be safely treated with IMT-alone.

Among patients for whom CABG was selected as the intended method of revascularization, the combination of prompt surgery and an insulin-sensitization strategy was associated with a lower rate of major CV events than any of the other treatment combination groups.

“This data may suggest that insulin-sensitization is preferable for patients with type-2 diabetes and coronary disease.”

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This complex trial was difficult to abstract clearly and concisely. I believe it does provide some guidance for primary care clinicians who may be negotiating with patients, in collaboration with their cardiologist consultants, about best therapy for this subset of diabetic patients.

1) Insulin-sensitization (metformin and thiazolidinediones) provides advantages over insulin-provision. (The study could not determine adverse effects of thiazolidinediones.)

2) If revascularization is advised, CABG is the preferred intervention. PCI is not recommended.

3) Intensive medical treatment alone is an option. Careful follow-up is required to determine if cross-over to CABG is necessary. As well as cross-over to additional drug therapy.

DIET

Behavioral Factors Rather Than Macronutrient Metabolism is The Main Influence on Weight Loss.

2-2 COMPARISON OF WEIGHT-LOSS DIETS WITH DIFFERENT COMPOSITIONS OF FAT, PROTEIN, AND CARBOHYDRATES
A crucial question is whether overweight people have a better response in the long-term to diets that emphasize a specific macronutrient composition—protein, fat, or carbohydrate.

Debate has been intense. Studies reach varying conclusions. Few studies extend beyond one year.

The authors of this study recognized the need for a large trial designed to overcome the limitations of previous trials, which would compare the effects of three principal dietary macronutrients. The trial lasted 2 years because weight loss typically is greatest 6 to 12 months after initiation, with steady regain in weight subsequently.

This randomized clinical trial assigned over 800 overweight and obese adults (mean age 50; BMI 33; about 2/3 female) to different diets and compared the effects on body weight of energy-reduced diets that differed in their targets for intake of macronutrients.

Randomly assigned to: Total fat (%) Protein (%) Carbohydrate (%)
1) Low-fat, average-protein 20 15 65
2) Low-fat, high-protein 20 25 55
3) High-fat, average-protein 40 15 45 (Close to a usual diet)
4) High-fat, high-protein 40 25 35

Group training sessions were held frequently. Daily meal plans were provided.

The goal for physical activity was 90 min of moderate exercise weekly.

Primary outcome = change in body weight over 2 years.

At 6 months, participants who completed the study had a mean weight loss of 6.5 kg. This corresponds to a reduction in daily energy intake of approximately 225 kcal. (The goal was a reduction of 750 kcal.)

After 12 months, participants began to regain weight.

Weight loss (kg) at 2 years:

<table>
<thead>
<tr>
<th>As originally assigned (n = 811)*</th>
<th>Completers at 2 years (n = 645; 80%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15% protein</td>
<td>3.0</td>
</tr>
<tr>
<td>25% protein</td>
<td>3.6</td>
</tr>
<tr>
<td>20% fat</td>
<td>3.3</td>
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<tr>
<td>40% fat</td>
<td>3.3</td>
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<tr>
<td>65% carbohydrate</td>
<td>2.9</td>
</tr>
<tr>
<td>35% carbohydrate</td>
<td>3.4</td>
</tr>
</tbody>
</table>

(*Intention-to-treat)

Differences between groups were not statistically significant.
Satiety, hunger, satisfaction with the diet, and attendance at group meetings were similar between diets.

At 2 years, waist circumference decreased by about 4 cm, with no statistically significant differences between groups.

The diets improved lipids and fasting insulin levels.

Attendance at group sessions strongly predicted weight loss.

“The findings should be directly applicable to both clinicians’ recommendations for weight loss in individual patients and the development of population-wide recommendations by public health officials”

Participants assigned to a high-fat average-protein diet [diet 3] above did not have to change their diet very much and could focus more on reducing caloric intake.

“We view attendance at counseling sessions as a proxy for commitment to achieving weight loss and for engagement in the program.” High attendees lost more weight and were less likely to regain after one year. Continued contact is essential.

“These findings point to behavioral factors rather than macronutrient metabolism as the main influences on weight loss.” Any type of diet, when taught for the purpose of weight loss with enthusiasm and persistence, can be effective. The specific macronutrient content is of minor importance. “Calories do count.”

Conclusion: Diets that are successful in causing weight loss can emphasize a range of fat, protein, and carbohydrate compositions that have beneficial effects. Such diets can be tailored to individual patients on the basis of their personal and cultural preferences and may have the best chance for long-term success.

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I congratulate the investigators on a study of importance to primary care. I hope the study will continue for another 5 to 10 years.

Overall, weight loss was disappointing, although there were a few outliers who lost a clinically significant amount of weight. Mean BMI declined from 33 to 31. Patients were still obese.

Primary care clinicians and their patients would rarely achieve even these limited results.

There were, however, occasional outliers who lost clinically significant weight.

We need a completely new societal approach to prevention of weight gain and to weight loss. What we have tried does not work. This would require a life-long population-based shift of dietary habits and exercise. This will not occur before the population becomes more educated and engaged. It must begin in childhood.
I enjoyed this article. It required hours for me to extract and condense meaningful aspects of the study. Authors and editors could publish data more clearly and concisely. They could present more detailed data in a linked web site.

DIFFICULT ENCOUNTERS IN PRIMARY CARE


2-4 BURDEN OF DIFFICULT ENCOUNTERS IN PRIMARY CARE

This study compared levels of stress, burnout, time pressure, and intent to leave practice between primary care physicians who report having high numbers of these patients and those who have fewer.

Physicians (n = 449; either general internists or family physicians) from 5 regions of the US responded to a “Difficult Doctor-Patient Relationship Questionnaire” Physicians were grouped into 3 clusters: those perceiving high, medium, and low numbers of difficult encounters.

The investigators identified eight types of difficult encounters.

Physicians who reported experiencing the highest difficulty with patient encounters were younger, more likely to be female, more likely to be internists than family physicians, to report burnout, to report job dissatisfaction, and to be more likely to leave the practice.

Physicians share responsibility with patients. Each contributes to such interactions.

Strategies to help physicians manage difficult encounters more effectively include: demonstrating more empathy; practicing nonjudgmental listening; providing more support to the physician by social service personnel; and allotting more time for patients likely to be difficult.

(See the following abstract.)

“Each Brings Something To The Table”

2-5 UNBURDENING THE DIFFICULT CLINICAL ENCOUNTER

Dealing with dysfunctional encounters is learned after medical school.

A more progressive view is that the problem is dyadic, a consequence of both patient and physician factors. Each brings something to the table.

We should be more circumspect about referring to the “difficult patient”, and refer to the event as a “difficult encounter” or a “difficult physician-patient relationship”.

What makes some encounters difficult?

Patient factors have been identified:

1) Psychological symptoms or disorders, especially somatization. And varying degrees of depression, anxiety, personality disorders, and substance abuse.
2) Patients who are “high users”, or “frequent attenders”.

Physician factors:

1) Psychosocial stress—burnout, job dissatisfaction, personal depression or anxiety,
   It is impossible to completely disentangle job and personal distress. Each has an adverse
   effect on the other. The unhappy physician may have a lower tolerance for complex or
   challenging encounters.

2) A bundled approach that tackles organizational, contextual, and physician factors may
   be more successful in unburdening difficult encounters than addressing only one factor.

What can we do to alleviate the problem?

1) Intensify physician training in psychosocial aspects of care. Psychosocially oriented
   physicians identify fewer encounters as difficult .

2) Identify, up front, patient’s expectations for the visit.

3) Accept the rough edges of the real world of practice. Do not take every difficulty personally.
   Concede that discordant encounters are inevitable.

4) Reform the context and reimbursements of primary care. Undervaluing cognitive services
   and “talk time” puts even greater pressure on the 15%-20% of visits considered difficult.

5) Celebrate a well-navigated difficult encounter. Dealing with difficulty signifies mastery
   rather than weakness. “Partnering with patients in the challenging aspects of their health,
   lives, or medical care is a stepping stone to surmounting together the difficult encounter.”

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I enjoyed these articles. this is the first time I remember reading abut these problems. They are
frequent in primary care medicine. I have experienced my share of difficult patients.

Looking back, I did indeed place the entire burden for the difficulty on the patient. I now recognize I
brought some difficulty too.

FAILURE TO INFORM PATIENTS

6-2 FREQUENCY OF FAILURE TO INFORM PATIENTS OF CLINICALLY SIGNIFICANT
OUTPATIENT TEST RESULTS

Failing to inform a patient about an abnormal outpatient test can be a serious error. Failure to inform
and failure to document that the patient has been informed are common and are legally indefensible
factors in malpractice claims.

This retrospective medical record review included over 5400 randomly selected records of primary
care outpatients (age 50-69) in 23 practices. Selected 11 blood tests and 3 screening tests
(mammography, Pap smear, and fecal occult blood test).

Defined a range of “clinically significantly abnormal” values for each test. These values were well out of the reference range, and almost all physicians would agree that the patient should be informed because the test indicated immediate danger, or had potential implications for health over time.

Good processes for managing test results: 1) all results are routed to the responsible physician; 2) physician signs off on all results; 3) the practice informs patients about all results, normal and abnormal; 4) documents that the patient has been informed; 5) patients are told to call after a certain time if they had not been notified.

Very few practices had explicit rules for managing test results.

Recorded 1889 abnormal test results. Of these there were 117 failures to inform, and 18 failures to document. Total of 135 of 1889 (7%).

Low process scores were significantly associated with failure to inform.

In 8 practices, patients were told that “no news is good news”—if patients did not hear about the test, they should assume it was normal. “No news is good news” is a dangerous practice.

Failure to inform could be approached as a systems problem—a problem of organization and incentives—rather than a failing of individual physicians.

Conclusion: Failure to inform patients, or to document informing patients of abnormal test results are common. Use of simple processes for managing results is associated with lower failure rates.

This is a good example of how a systems approach may improve methodology. Primary care practices should adopt good processes, not leave it to the individual physician.

Adding an EMR to poorly organized systems may make things worse.

Patients frequently wait for reports with anxiety. Poor communication remains a major fault in medicine. I believe prompt reporting is a manifestation of caring.

FIBROMYALGIA

Antidepressants Were Associated With Improvement.

1-6 TREATMENT OF FIBROMYALGIA SYNDROME WITH ANTIDEPRESSANTS: A Meta-analysis

FMS is described as chronic widespread pain with a minimum of 11 of 18 defined tender points. Fatigue and non-restorative sleep are common. Most patients report additional somatic and psychological symptoms.
This systematic review determined efficacy of antidepressant drugs in the treatment of FMS. The goals of the study were: 1) to evaluate effects of treatment of FMS-related symptoms; 2) to determine internal validity (methodological quality); and 3) external validity (generalizability). It included 18 randomized, controlled trials of antidepressants prescribed for outpatients. (Mean duration = 8 weeks; mean age = 47; mostly female) None had severe somatic disease.

“We found strong evidence for the efficacy of antidepressants in reducing pain, sleep disturbances, depressed mood, and for improving HRQOL.”

This meta-analysis does not allow a definitive conclusion regarding superiority of one class of antidepressant over another. However, duloxetine is the only one the FDA approves for treating FMS. Only duloxetine has demonstrated efficacy for FMS patients with, as well as without, major depressive disorder.

The internal and external validity of the RCTs analyzed was limited.

Short-term use of amitriptyline and duloxetine can be considered for the treatment of pain and sleep disturbance in patients with FMS—based on the number of patients studied (duloxetine) and the effects size (amitriptyline).

Goals of treatment should be defined (no cure, but possible symptom reduction). Evidence of long-term effects is lacking.

Conclusion: In patients with FMS, antidepressants are associated with improvements in pain, depression, fatigue, sleep, and HRQOL.

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This meta-analysis provides primary care clinicians with nebulous data and nebulous guidance.

Primary care clinicians and their patients must rely on trial and error when applying antidepressant therapy for FMS. Individual patients should be informed about risks and benefits in order to make an informed choice about whether they wish to start drug therapy. They should be informed at outset that therapy will not cure—it may improve symptoms.

With so many drugs available—where to start? I believe a reasonable choice would be amitriptyline, given in low dose at bedtime.

GUIDELINES

The Gap Between The Standards Set In CVD Prevention Guidelines And Clinical Practice Continues.

3-2 CARDIOVASCULAR PREVENTION GUIDELINES IN DAILY PRACTICE [See CARDIOVASCULAR DISEASE]
HEART FAILURE

“NSAIDs Should Be Avoided In All Patients With HF.”

1-3 INCREASED MORTALITY AND CARDIOVASCULAR MORTALITY ASSOCIATED WITH USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN CHRONIC HEART FAILURE

Accumulating evidence indicates there is an increased cardiovascular risk associated with NSAID use, particularly in patients with established cardiovascular disease (CVD).

NSAIDs are available OTC and are used by many elderly patients. The widespread use of NSAIDs and the general perception that they are low-risk drugs prompted this study.

Entered (in 1993-2004) and followed over 107 000 patients (mean age 75) who had survived their first hospitalization for heart failure (HF). Determined subsequent use of NSAIDs from the nationwide registry of Denmark. A total of over 36 000 patients claimed at least one prescription for NSAIDs after discharge. Determined total deaths, and hospitalizations from HF and myocardial infarction over a 10 year period.

A total of 60 974 patients died during the study. The hazard ratio for death in those taking a NSAID (compared with taking no NSAID) was: diclofenac 2.08; celecoxib 1.75; rofecoxib 1.70; ibuprofen 1.31; naproxin 1.22.

There was an increased risk of death associated with most NSAIDs. Risk highest for rofecoxib, celecoxib, and diclofenac.

There was a clear dose-dependent increase in risk. Low doses of ibuprofen (under 1200 mg/d) and naproxin (under 500 mg/d) were not associated with increased mortality. Higher doses were associated with increased risk.

Hospitalizations because of MI (9%) and HF (37%) increased in a dose-dependent manner with use of both selective and non-selective NSAIDs. Hazard ratios were similar for all types except for rofecoxib, which was associated with the highest risk in a dose-dependent manner.

“We found increased mortality and increased risk of hospitalization for MI or HF related to use in an unselected cohort of patients discharged alive after their first hospitalization because of HF.”

Conclusion: Treatment with NSAIDs, both selective and non-selective, in patients with chronic HF is associated with increased mortality and cardiovascular morbidity in a dose-dependent manner.

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HF patients who persist in using NSAIDs should be advised to use ibuprofen or naproxin in low doses.
Diclofenac, naproxin, and ibuprofen are much cheaper (compared with OTC price) when purchased by prescription at several pharmacies offering prescriptions at $4.00 for a 30-day supply and $10.00 for a 90-day supply.

HUMAN IMMUNODEFICIENCY SYNDROME (HIV)

Is This A Reasonable Recommendation For Primary Care?

1-7  CLINICIANS ADVISED TO STEP UP HIV TESTS

An estimated one million individuals in the US have human immunodeficiency virus (HIV) infection. Of these, about 20% are not aware of their status.

Experts on HIV/AIDS care have called upon health care professionals to follow federal recommendations (issued more than 2 years ago by the CDC) that call for routine HIV testing all patients age 13 to 64. (Patients are given an opportunity to opt out of the test. RTJ)

Rapid screening saliva test is highly sensitive and specific. “The test is cheap, and easy. It’s almost perfect in terms of getting positive or negative results. If positive, it requires confirmatory testing.

“Testing for HIV should be as routine as the flu shot”.

HIV infection can be approached as a chronic, rather than a fatal illness. Routine testing could help tens of thousands receive lifesaving treatment while preventing new infections. These individuals are more likely to transmit their infection to others.

Lack of reimbursement by insurers is a barrier to testing. Medicare and Medicaid do not routinely reimburse.

The recommendation has not been widely implemented by clinicians.

JAMA January 28, 2009; 301: 366 “Medical News and Perspectives” by Rebecca Voelker, JAMA staff.

The State of North Carolina has changed the rules for testing: eliminating the requirement for pre-test counseling, and post-test counseling for those with a negative test. HIV test can be included in a panel of tests using a general consent for treatment. Ie, the patients must be notified that they will be tested, but a specific consent for testing is not required.

I can think of reasons why testing is not implemented in primary care.

1) Time: Explaining the reason for the procedure, as well as performing it, requires time primary care clinicians can ill afford

2) If one million patients in the US have HIV, and 20% are not aware of it, then only 200 000 individuals have unknown HIV. To discover them, about 200 million individuals need be tested at a considerable cost. I believe a more reasonable course would be to test selected
patients—those who would be more likely to harbor HIV. Testing select patients in emergency departments would be reasonable.

3) How much does the test cost? Who pays? Would a 60 year old lady be offended when she is billed for a HIV test?

4) Is one-time testing the recommendation? How about the many individuals who might acquire the infection after the first test?

5) False positives: No matter how high the specificity of the test, when a large number of individuals are tested, some false-positives will occur. This leads to confirmatory testing with added time spent, added expense, and a high degree of anxiety.

**HUMAN PAPILLOMA VIRUS (HPV)**

_The Quadrivalent HPV Vaccine Was Efficacious In Women Age 24-45_

6-5 SAFETY, IMMUNOGENICITY, AND EFFICACY OF QUADRIVALENT HUMAN PAPILLOMAVIRUS (TYPES 6, 11, 16, 18) RECOMBINANT VACCINE IN WOMEN AGE 24-45

Women older than age 25 clearly retain a substantial risk for acquisition of HPV. The extent to which infections occurring in mid-adult life are associated with subsequent risk of precancer and cancer is not clear.

The peak incidence of HPV infection occurs within 5-10 years of first sexual experience. A second peak has been recorded in women age 30-50. Whether this second peak is due to reactivation of latent infections, or new HPV infections is not clear. There is a possibility of new infections.

This international randomized, double-blind, placebo-controlled trial entered 3819 women age 25-45 between 2004-2006. None had a history of genital warts or cervical disease. None were pregnant or immunocompromised.

Randomized to: 1) Aluminum adjuvant quadrivalent vaccine (Gardisil; Merck), or 2) Aluminum containing placebo injection. Injections were given at day 1, and months 2 and 6.

Performed gynecological examinations periodically up to 48 months. Specimens were tested by PCR for HPV DNA. Also tested subjects for infection by a serological test (immuno-assay for antibodies to HPV).

At baseline, HPV positivity to either 6, 11, 16, or 18 by immunoassay or DNA testing was 33%. 90% of women were naïve to 3 vaccine types; 66% were naïve to all 4 types.

Almost all women seroconverted. Those who were infected with one type at baseline usually experienced a rise in titer to that type.
Vaccine efficacy:

A. Against incidence of infection (detected by serology) = 93%.
   Infection occurred in 3 vaccine subjects vs 40 placebo subjects.
B. Against clinical disease (detected by PCR): one vaccine vs 13 placebo cases.
C. Against combined incidence of infection or clinical disease related to types 16 and 18 = 83%;
   4 cases in the vaccine group vs 23 cases in the placebo group.
D. Against types 6 and 11 = 100%; 0 in the vaccine group and 19 in the placebo group.

Adverse effects: 5 persons in the vaccine group and one in the placebo group discontinued because of adverse effects. No serious vaccine-related adverse events were recorded.

“Our results are generalizable to women aged 24-45 years in the general population who have had no (recent) cervical disease and no previous history of external genital disease.”

Conclusion: The quadrivalent HPV vaccine was efficacious in women age 24-45 who were not infected with the relevant HPV types at enrollment.

This trial was conducted in 6 different countries. This is an excellent illustration of international cooperation. I congratulate all concerned.

In those already infected with one type, titers of antibodies to that type rose after administration of the vaccine. Will this help eliminate the infection? Previous studies of HPV stated the vaccine was not therapeutic.

This application is not ready for prime time. We await developments with interest.

This may prove to be a major advance in cancer prevention.

The duration of immunity is not known. Boosters may be required.

HUMANISM IN MEDICINE

The Other Side of the Coin

6-1 THE SILENT DIMENSION: Expressing Humanism in Each Medical Encounter

Professional competence encompasses two sides of the same coin: professional skills (disease oriented) and humanistic values (patient oriented).

“Humanistic medicine” has a number of meanings. It centers around the physician’s comprehension of the patient’s narrative and emotions; compassion, and commitment to act and try to alleviate the patient’s suffering. Humanistic behavior is an essential component of professional medical care. It is often neglected. Sincere humanistic behavior can become an integral part of the encounter, correct current deficiencies, and catch up with the astounding advances in modern biomedicine.
A warm, interested and supportive attitude toward the patient can be adopted with ease at every setting. Inclusion of the humanistic aspect of each physician-patient encounter may significantly alter the current scene. Marked benefits for both physician and patient can be expected, including patient’s satisfaction, trust, and compliance, leading to better health outcomes.

The commentator suggests use of a simple mnemonic for clinicians to capture and apply the essentials of a humanistic physician-patient relationship.

**CAPTURES:**

- **Curiosity:** about the patient’s personal aspects.
- **Admire:** finding something to admire about the patient.
- **Perspective:** try to see things from the patient’s point of view.
- **Touch and Use:** body language (proximity, holding the patient’s hand, smile) to convey caring and attention.
- **React:** to what the patient says and does, and how. Take notice!
- **Support:** Stress any positive or encouraging aspects to provide support and reassurance.

Humanism can be taught and acquired. Lack of training constitutes one of the worst barriers to implementation. A warm, attentive, personal, and caring attitude on the part of the physician can be easily achieved and incorporated into the encounter.

Read the full abstract

I do not recall any discussion about the humanistic aspects of medicine during my training years (admittedly years ago). I believe it is stressed in training programs now. I hope so. Looking back, during my active practice years, I almost always focused more on the disease. I was intent on not missing any important diagnosis and providing the most effective medical treatment. If I could do it over again, I would certainly focus equally on the patient side. I believe I would then be a more productive clinician, and my practice would be more enjoyable.

HYPERTENSION

*Questions and Answers from A National Conference*

**2-9 BLOOD PRESSURE SELF-MONITORING**

BP monitors are inexpensive. They are now used by many patients with in the USA to self-monitor BP (SMBP).
This review, based on available evidence from randomized trials, systematic reviews and expert consensus, discusses the critical importance of SMBP in establishing the diagnosis of hypertension, subsequent titrating drug treatment, and long-term monitoring.

BP can vary widely. SMBP allows multiple measurements and therefore provides a more precise measure of “true” BP, and information on the variability of BP.

Integrating SMBP into daily practice requires appropriate equipment, systems, and education—of patients and their doctors.

This article reviews many questions asked about SMBP. (Please red the full abstract.)

Summary:
SMBP readings are usually lower than office readings.
SMBP is useful in the diagnosis and management of hypertension.
Multiple measurements allow a better estimation of “true” BP.
SMBP correlates better with risk of stroke than office readings.
Patient education and clinically validated monitors are prerequisites.

What needs confirmation:
How should SMBP be used as opposed to office management to assess risk of cardiovascular disease?
Should SMBP be intermittent (6 monthly) or weekly?
What is the effectiveness and the cost-effectiveness of treatment based on SMBP vs standard care?
What is the effect of SMBP on long-term BP control?

The critical question remains: Does SMBP, compared with office BP, further reduce risk of stroke, myocardial infarction and heart failure?

I believe many patients and health care workers do not realize how variable BP is. We depend on average readings at rest. Many office visits begin with a BP reading by an office nurse taken only once. The nurse then states, “Your BP is . . .”

SMBP has the advantage of allowing adjustment of dose of anti-hypertension drugs. Lowering the dose is just as important as raising the dose.

Despite the widespread use of BP-lowering drugs and the results from many randomized trials, uncertainty remains about which drugs to use, and who to treat.

Five questions encapsulate the uncertainty:

1. Do beta-blockers have a special effect over and above lowering BP in preventing coronary heart disease (CHD) events in people with a history of CHD?
   Yes. The effect is an approximate 30% reduction in CHD, present for a few years after the infarct. This risk reduction is about 15% thereafter, similar to that of other BP lowering drugs.

2. Does the effect of BP-lowering drugs in preventing CHD and stroke differ in people with and without a history of cardiovascular disease? (i.e., is there a different effect in secondary and primary prevention?)
   No. The percentage reduction in risk of CHD events and stroke is the same or similar. Since the absolute risk is highest in people with a history of cardiovascular disease, the absolute risk reduction is greater.

3. Does BP reduction alone explain the effect of BP-lowering drugs in preventing CHD and stroke?
   Yes, except for the special short term effect of beta-blockers.

4. Should the use of BP-lowering drugs be limited to people with “high” BP?
   No. BP lowering drugs should be offered to anyone with a high enough risk to benefit from treatments whatever the reason for being at high risk, because a given blood pressure reduction lowers risk of CHD and stroke by a constant relative \( (\text{but not absolute}) \) proportion irrespective of pretreatment blood pressure.

5. What is the quantitative effect of taking one or more BP-lowering drugs in lowering BP and preventing CHD events and stroke according to dose, pretreatment BP, and age?
   In people age 60-69, with a diastolic of 90 or systolic of 150, one drug at standard dose lowers the risk of CHD by about 25%, and of stroke by about 35%. Three drugs at half standard dose lower the risk of CHD by about 45% and of stroke by about 60%. The estimates are about 10 percentage points higher if blood pressure is higher by 30/15. The estimates are about 5 percentage points lower for a 10 year increase in age.
These investigators answered these questions using the results of 147 randomized trials of BP-lowering drugs and CHD events (n = 22,000) and stroke (n = 12,000), and correlated their results with several large previously published meta-analyses. They also quantified the effect of BP-lowering drugs on the incidence of heart failure, cancer mortality, and other non-vascular mortality, and all-cause mortality.

This is a large, complex meta-analysis. The abstract is by far the longest I have ever written. And the most difficult.

I believe its length is justified by its importance to primary care. The authors present some novel and, I believe, controversial arguments about lowering BP, some of which would represent a sea-change in our approach to treatment of blood pressure.

Please read the full abstract.

What change from our present approach does this study suggest? Should we change our approach?

How would I respond to their suggestions?

1. The study is based on relative risk reductions. To apply to primary care patients, we must rely on absolute risk reductions in individuals as related to age and past history of CHD and stroke and other factors.

2. Response to antihypertension therapy will vary from patient to patient. Individualization is required.

3. The observation that all 5 drugs are equally effective in lowering BP will enable freer choice according to patients’ response and preference.

4. Early on, I would prescribe a combination of low dose drugs. There is strong evidence that a combination of 2 or 3 drugs at low dose is more effective than one drug at higher dose, and the combination is safer.

5. I would be more aggressive in lowering BP in patients at higher risk because of age or past history. This would extend to those with a BP well below the cut point of 140/90.

6. BP is not the only risk factor to reduce. Lowering other risk factors will modify the effect of lowering BP.

7. Patients should be followed for effectiveness and adverse effects. Individual patients will vary.

8. I would be more willing to cautiously prescribe beta-blockers for patients with heart failure and post-myocardial infarction.
**HYPERTHYROIDISM**

**6-10 RECENT DEVELOPMENTS IN HYPERTHYROIDISM**

Since the 2003 *Lancet* seminar on hyperthyroidism, several reports have enhanced understanding of the end-organ manifestations of hyperthyroidism.

This brief article comments on:

1. Atrial fibrillation in older persons with subclinical hyperthyroidism (SCH).
2. Relation of SCH to all-cause mortality
3. Treatment of SCH in asymptomatic patients
4. Bone loss associated with SCH
5. Sexual dysfunction in males with hyperthyroidism
6. Antithyroid drugs to treat hyperthyroidism. Methimazole may be preferable to propylthiouracil
7. Antithyroid drugs as definitive treatment of Graves disease.
8. Antithyroid drugs prior to radio-iodine treatment
9. Long-term quality of life of patients with Graves disease

Please read the full abstract.

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1. The FDA has recently alerted physicians about the risk of liver failure and death in patients taking propylthiouracil for Graves disease. Of 32 patients taking propylthiouracil who developed a serious liver injury, 13 died, and 11 required liver transplant. Only 5 cases of liver failure from methimazole have been reported. Patients taking propylthiouracil should be closely monitored for signs of liver injury. Propylthiouracil should be avoided unless there are no other options.

*JAMA “Medical News and Perspective” July 20/29 302; 370-71*

This is amazing! Propylthiouracil has been prescribed for decades. There must be many drugs causing serious effects we know nothing about.

**INFLUENZA**

*A H1N1 Influenza Center At NEJM.Org Will Help Monitor The Disease*

**6-7 H1N1 INFLUENZA A—INFORMATION FOR HEALTH PROFESSIONALS**

In the first 2 weeks in April 2009, cases of an untyped influenza A began to be identified in Mexico and Southern California. By the third week in April, it was established that the illness resulted from a triple recombination of human, avian, and swine influenza viruses. It is an H1N1 virus.
A polymerase-chain-reaction (PCR) has been developed, which enables determination whether an illness with the protean manifestations of cough, fever, sore throat, diarrhea, and nauseas, could be confirmed as a case.

By May 7 (only one month after the first case) articles appeared providing background information about the novel virus in the USA. The goal was to provide clinical descriptions of patients so that health professionals could make the difficult decision about whether an individual had a suspected case. The decision depends on the presence of typical, but unfortunately variable and non-specific symptoms. Identifying a case by PCR allows epidemiological links to be established.

The ability to clearly define a confirmed case will allow for a careful assessment of the associated illness and its severity. We now have important tools to fight this outbreak: a clear definition, an aware health care system, and an informed public.

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*Please read the full abstracts.*

*I believe the identification, tracking, and prompt notification of this disease is a miracle of modern technology and a source of satisfaction to the WHO, the CDC and the Public Health Service*

*Would outcomes have been different if this technology were available in 1918?*

**The Current Situation Is Not “1918 Again”. It Is 1918 Continued.**

**6-8 IMPLICATIONS OF THE EMERGENCE OF A NOVEL H1 INFLUENZA VIRUS**

A group of viruses, called triple reassortants of viruses from pigs, humans, and birds (triple reassortant swine influenza A (H1) viruses) has circulated among pigs for more than a decade. These viruses may occasionally be transmitted from pigs to humans, but do not spread efficiently from human to human.

Another group is a recent reassortant of the triple swine influenza A virus (H1) and an Eurasian swine influenza virus. This new virus is the H1N1 currently being transmitted human to human and has spread rapidly to many countries.

It is termed the swine-origin influenza virus (S-OIV)

The current situation is not “1918 again”. It is 1918 continued. We are being infected with the remnants of the 1918 virus.

Questions remain:

1) Will S-OIV replace human H1 virus as the seasonal virus and evolve antigenic variants every year?
2) Will S-OIV further adapt to humans and become more severe?
3) Will it return in the fall season and become more severe with higher mortality?
4) Will a vaccine be available? Development will be challenging.

IRRITABLE BOWEL DISEASE

Should Primary Care Physicians Test Patients With IBS For CD?

4-4 YIELD OF DIAGNOSTIC TESTS FOR CELIAC DISEASE IN INDIVIDUALS WITH SYMPTOMS SUGGESTIVE OF IRRITABLE BOWEL DISEASE  [See CELIAC DISEASE]

MEAT INTAKE AND MORTALITY

Red Meat Associated with Increases in Total, Cancer, and CVD Mortality

3-4 MEAT INTAKE AND MORTALITY: A Prospective Study of Over Half a Million People

This study assessed the relation between red, white, and processed meat on the risk of total mortality and cause-specific mortality. It included about half a million men and women enrolled in the National Institutes of Health—AARP Diet and Health Study.

Recruited individuals age 50 to 71 for 6 states and two metropolitan areas. After exclusions, the analytic cohort included 322,265 men and 223,390 women.

At baseline, all completed a 124-item questionnaire on demographic and lifestyle characteristics, including dietary habits.

Meat intakes based on quintiles of red meat intake in men:

<table>
<thead>
<tr>
<th></th>
<th>Q1</th>
<th>Q5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red meat g/1000 kcal</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td>White meat g/1000 kcal</td>
<td>37</td>
<td>31</td>
</tr>
<tr>
<td>Processed meat g/kcal</td>
<td>5</td>
<td>19</td>
</tr>
</tbody>
</table>

Intakes was similar in women.

During 10 years of follow-up, there were 47,976 male deaths, and 23,276 female deaths.

Mortality in men (Hazard ratios—adjusted):

A. Red meat intake
   - All deaths 1.00 1.31
   - Cancer deaths 1.00 1.22
   - CVD deaths 1.00 1.27

B. White meat intake
   - All deaths 1.00 0.92
Mortality in women was similar.

“We found modest increases in risk for total mortality, as well as cancer and CVD mortality, with higher intakes of red and processed meat.”

In contrast, higher white meat consumption was associated with a small decrease in total and cancer mortality.

CONCLUSION: Higher red and processed meat intakes were associated with modest increases in total, cancer, and cardiovascular mortality. High white meat intake was associated with a small decrease in total and cancer mortality.

----------

_I believe primary care clinicians may reasonably advise patients about these dietary restrictions. It joins other important beneficial life-style modifications. Primary care clinicians should adopt healthy lifestyles themselves._

**NSAIDs**

“**NSAIDs Should Be Avoided In All Patients With HF.**”

**1-3 INCREASED MORTALITY AND CARDIOVASCULAR MORTALITY ASSOCIATED WITH USE OF NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN CHRONIC HEART FAILURE**

Accumulating evidence indicates there is an increased cardiovascular risk associated with NSAID use, particularly in patients with established cardiovascular disease (CVD).

NSAIDs are available OTC and are used by many elderly patients. The widespread use of NSAIDs and the general perception that they are low-risk drugs prompted this study.

Entered (in 1993-2004) and followed over 107 000 patients (mean age 75) who had survived their first hospitalization for heart failure (HF). Determined subsequent use of NSAIDs from the nationwide registry of Denmark. A total of over 36 000 patients claimed at least one prescription for
NSAIDs after discharge. Determined total deaths, and hospitalizations from HF and myocardial infarction over a 10 year period.

A total of 60,974 patients died during the study. The hazard ratio for death in those taking a NSAID (compared with taking no NSAID) was: diclofenac 2.08; celecoxib 1.75; rofecoxib 1.70; ibuprofen 1.31; naproxin 1.22.

There was an increased risk of death associated with most NSAIDs. Risk highest for rofecoxib, celecoxib, and diclofenac.

There was a clear dose-dependent increase in risk. Low doses of ibuprofen (under 1200 mg/d) and naproxin (under 500 mg/d) were not associated with increased mortality. Higher doses were associated with increased risk.

Hospitalizations because of MI (9%) and HF (37%) increased in a dose-dependent manner with use of both selective and non-selective NSAIDs. Hazard ratios were similar for all types except for rofecoxib, which was associated with the highest risk in a dose-dependent manner.

“We found increased mortality and increased risk of hospitalization for MI or HF related to use in an unselected cohort of patients discharged alive after their first hospitalization because of HF.”

Conclusion: Treatment with NSAIDs, both selective and non-selective, in patients with chronic HF is associated with increased mortality and cardiovascular morbidity in a dose-dependent manner.

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HF patients who persist in using NSAIDs should be advised to use ibuprofen or naproxin in low doses.

Diclofenac, naproxin, and ibuprofen are much cheaper (compared with OTC price) when purchased by prescription at several pharmacies offering prescriptions at $4.00 for a 30-day supply and $10.00 for a 90-day supply.

**OBESITY**

*Weight Reduction Was Associated With A Decrease In Incontinence*

1-4 **WEIGHT LOSS TO TREAT URINARY INCONTINENCE IN OVERWEIGHT AND OBESE WOMEN** (See URINARY INCONTINENCE [1-4])

**OSTEOPOROSIS**

*Associated With Increased Mortality Risk*

2-3 **MORTALITY RISK ASSOCIATED WITH LOW-TRAUMA OSTEOPOROTIC FRACTURE**
The premature mortality following hip and vertebral fractures is well known. Premature mortality following other fracture types is less well appreciated.

This study examined: 1) the long-term mortality risk following all types of osteoporotic fracture in men and women in different age groups [all over age 60]; 2) the association of a subsequent (a second) fracture with that mortality risk; 3) what clinical factors present at the time of fracture predict mortality; 4) the effect of fracture on mortality over and above the effect of low bone mineral density (BMD).

In the small community of Dubbo Australia (entire population over age 60 = 4005), between 1989 and 2007, 952 women (42%) and 343 (17%) men sustained at least one minimal-trauma fracture. Of those who sustained a fracture, 47% (n = 614) agreed to participate in a detailed on-going assessment. High-trauma fractures; potentially pathological fractures; and fractures of the head, fingers, and toes were excluded. The study included only fractures considered to be osteoporotic (fragility fractures).

Median follow-up after the fracture was 12 years.

For each age group, mortality rates in those who sustained a fracture (in both sexes) were consistently higher over the following 5 years than in the general population.

<table>
<thead>
<tr>
<th>Mortality rates in women</th>
<th>Per 100 person years</th>
<th>Mortality ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>General population</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>All fractures</td>
<td>7.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>15</td>
<td>2.4</td>
</tr>
<tr>
<td>Vertebral fracture</td>
<td>9</td>
<td>1.8</td>
</tr>
<tr>
<td>Major* fracture</td>
<td>7.8</td>
<td>1.7</td>
</tr>
<tr>
<td>Minor** fracture</td>
<td>5</td>
<td>1.4</td>
</tr>
</tbody>
</table>

(* Major included pelvis, distal femur, proximal tibia, 3 or more ribs, and proximal humerus. ** Minor all other osteoporotic fractures.)

Rates in men were higher.

A first fracture was associated with 2- to 4-increased risk of a second fracture. This contributes to the morbidity and mortality burden of fragility fractures. Following a second fracture, the death rate was elevated for another five years.

Major causes of death were the same as in the general population.

Those with fractures who died were older, had smoked, weighed less, had lower bone density, weaker quadriceps, and decreased physical activity.

When women without fracture were matched by age and BMD with women with fracture, there was no difference in mortality. Thus, in the group of women without fracture, low BMD per se was an underlying high mortality risk.
A subsequent (second) fracture is clearly an additional risk factor for premature mortality. Its prevention may contribute to a decrease in overall excess mortality.

Conclusion: Low-trauma fractures in older men and women were associated with increased mortality risk for 5 to 10 years. A second (subsequent) fracture increased mortality for an additional 5 years.

This presents a splendid challenge and opportunity for primary care, especially when “The Primary Care Medical Home” becomes more common.

Preventive therapy of osteoporosis, when begun in earlier life, will shorten the length of disability and dependence, and will lengthen the health-related quality-of-life. It will reduce morbidity, and costs of medical and social care.

Go into elderly life with strong bones!

“Is Potentially Misleading and A Misuse Of Healthcare Resources”

6-4 MONITORING BONE MINERAL DENSITY DURING ANTIRESORPTIVE TREATMENT FOR OSTEOPOROSIS [See BONE MINERAL DENSITY]

PERIPHERAL VASCULAR DISEASE

The Current Evidence Is Insufficient To Rule Out A Small Yet Important Benefit

5-4 ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE: [See ASPIRIN]

PNEUMONIA VACCINE

1-9 CDC PANEL RECOMMENDS PNEUMONIA VACCINE FOR SMOKERS.

The CDC Advisory Committee on Immunizations advises: “All smokers (age 19-64) should receive the 23-valent pneumococcal vaccine.” This is the first time smokers have been targeted for vaccination.

Smokers are at increased risk of developing pneumococcal disease. More than half of adults with pneumococcal disease are current or former smokers.

Smoking can cause structural changes in the respiratory tract that may make individuals more vulnerable to respiratory infections (bacterial and viral). It can also dampen immune response systemically and locally within the lungs. *S pneumoniae* may adhere more readily to the epithelial cells of smokers.

There is evidence that cessation can reduce risk of respiratory infections.
All individuals over age 65, as well as those with asthma and COPD, should receive the vaccine. Many smokers may have been covered by previous recommendations.

JAMA December 17, 2008; 300: 2713 “Medical News and Perspectives” by Bridget M Kuehn, JAMA staff.

POLYPILL

An Inexpensive, Convenient Way To Reduce Multiple Risk Factors For Cardiovascular Disease

4-3 EFFECTS OF A POLYPILL (Polycap) ON RISK FACTORS IN MIDDLE-AGED INDIVIDUALS WITHOUT CARDIOVASCULAR DISEASE

Low-dose aspirin, beta-blockers, antihypertension drugs, and statins—each reduces incidence of cardiovascular disease (CVD). One combination pill including all drugs could potentially reduce incidence of CVD more efficiently and cheaply than each drug given separately.

Can one pill deliver an effect similar to the additive effects of each component given separately? What degree of reduction in BP and LDL-cholesterol can be achieved in people with “normal” levels? Will the pill be well tolerated? Do unexpected interactions occur when these drugs are given in a single pill? Does aspirin reduce the BP-lowering effect of antihypertension drugs?

The pill (actually a capsule) contained 5 drugs (all generics): 3 antihypertension drugs (thiazide, beta-blocker, and ACE inhibitor); a statin; and aspirin, all in low doses (except atenolol): hydrochlorothiazide, 12.5 mg; atenolol 50 mg; ramipril 5 mg; simvastatin 20 mg; and aspirin 100 mg.

Recruited over 2000 individuals ages 45-80, who had no history of CVD. All had at least one risk factor for CVD.

Randomly assigned individuals into one of nine groups; 412 received the Polycap (5 drugs); 8 groups of 200 each received various combinations of 1, 2, 3, or 4 drugs.

Effect on BP: The Polycap (3 antihypertension drugs) reduced BP by about 7/5 mmHg—a greater reduction than any combination of 2 other antihypertension drugs. A subgroup analysis compared effect of the Polycap on patients with BP under 140 and over 140. Systolic was reduced by 6/5 mmHg in the former group, and by 8/6 mm Hg in the latter.

Lipids: LDL-cholesterol was reduced slightly more in the simvastatin-alone group than in the Polycap group (-32 mg/dL vs -27). The effect of simvastatin in lowering LDL-c was evident in participants with levels below the median as well as in those above the median (-25 mg/dL in the former vs -36 mg/dL in the latter). In diabetic patients, both the absolute and proportionate LDL-c reduction was greater than in those without diabetes.
Heart rate: Reduced by 7 beats per minute in both Polycap and atenolol alone groups.

Urinary thromboxane (effect of aspirin): Any group containing aspirin alone or aspirin + BP drugs lowered thromboxane by 348 ng/mmol creatinine vs 283 for Polycap.

Adverse effects: Withdrawals overall = 15%, mainly because some participants perceived little benefit. Rates and reasons for discontinuation were similar across all 9 groups; drug-specific adverse effects in 4% overall.

Adverse effects in the Polycap group: dizziness/hypotension 6%; cough 5%; fatigue 2%; creatinine increase over 50% 9%; SGPT doubled 3%.

Tolerability and safety were similar to that of single low-dose drugs, suggesting no increase in drug-specific adverse effects of the Polycap. “An analysis by one or more active components in the pill suggests similar rates of drug discontinuation, allaying concern that the Polycap would have increased rates of side-effects and intolerability as the number of components increased.”

Conclusion: This formulation could be inexpensive, and conveniently used to reduce multiple risk factors for cardiovascular disease.

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The polypill concept is intriguing. Interest seems to continue. I doubt the concept will die.

At present, millions of patients in the USA are already taking several, or all, of the individual prescription drugs. This adds expense and inconveniences.

“Risk Factor Thresholds: Their Existence under Scrutiny” Law and Wald BMJ 2002 324; 1570-76

Interventions to lower BP, cholesterol, and other risk factors reduce the risk of CVD regardless of initial levels. The goal is not to “normalize” risk factors, but to reduce them as much as possible. This means targeting all risk factors for everyone at risk, rather than by the level of the risk factor.

A given reduction in the risk factor reduces risk of disease by a constant proportion of the existing risk regardless of the initial level of the risk factor.


The original concept of the polypill was proposed by Wald and Law. They based their concept on the observation that, regardless of initial levels of risk factors, even if within “normal” limits, lowering them further (down to an undetermined level) leads to an absolute and proportional reduction in risk. (By this criterion, all persons in developed countries have some risk factors.)

This original article suggested giving a daily combination of low-dose drugs to all individuals 55 years of age and older—without prescreening and follow-up This could be a means of reducing risk of
CVD in the general population. The lower the risk factor, the lower the risk of disease down to levels well below average Western values. BP-lowering should not be limited to people with “high blood pressure”, nor lowering cholesterol levels limited to people with “high cholesterol”. The constant proportional relation means there is value in modifying risk factors regardless of the level of the risk factor. All reversible risk factors should be changed, not just those judged “abnormal”.

Adverse drug effects are much lower when low doses are given than when average doses are given.

Our terminology now regards extreme values as indicating a diseased state (hypertension; hypercholesterolemia; osteoporosis; obesity) and average values as being “normal” (normotensive; normocholesterolemic) Clinical guidelines specify risk factor thresholds.

“Normal” levels are arbitrary and artificial.

PREDIABETES

Public Awareness Of PD Is Very Low

2-6 SELF-REPORTED PREDIABETES AND RISK-REDUCTION ACTIVITIES: 2006

At least one fourth of U.S. adults are known to have prediabetes (PD), defined as having impaired fasting glucose (100 mg/dL to 125 mg/dL after an overnight fast), impaired glucose tolerance (plasma glucose 140 to 199 in a 2-hour oral glucose tolerance test), or both.

These persons are at risk for developing type-2 diabetes, heart disease, and stroke.

Public awareness of PD is very low. A CDC analysis of data collected in 2006 found that only 4% of 24,000 adults knew they had PD. Most of these were told they had “borderline diabetes”. The actual prevalence is about 40% in adults age 40-70.

Most patients with PD do not exercise adequately, do not control their weight or restrict fat and calories.

The Diabetes Prevention Program Intervention Trial showed that diet and exercise can lower the incidence of type-2 diabetes by 58% over 3 years among those at high risk. The American Diabetes Association recommends that patients with PD lose 5-10% of body weight, and increase physical activity to at least 150 minutes of moderate exercise weekly.

The article includes criteria for screening. (See the full abstract) It concludes by advising all persons over age 45 to be screened.

---------

I would not label persons with PD as having “borderline diabetes” I would try to explain that they have difficulty metabolizing sugar. They are overloading their body with excess food.

Labeling may increase anxiety and have a negative effect on employment and insurance.
This is a perfect opportunity and challenge of primary care medicine. With the advent of a “medical home”, which will increase closer follow-up and continued communication, prevention and treatment of PD can become more efficient. This would lower future costs of care and prolong quality-years-of-life.

PROSTATE CANCER

“The Key Question Is Not Whether PSA Screening Is Effective, But Whether It Does More Good Than Harm.”

3-6 SCREENING FOR PROSTATE CANCER: The Controversy That Refuses to Die

In the US, most men over age 50 have had a prostate-specific antigen (PSA) test despite the absence of evidence from large, randomized trials of a net benefit. About 95% of urologists and 78% of primary care physicians age 50 and over report that they have had a PSA test themselves.

And indeed, US death rates from prostate cancer (PC) have fallen about 4% per year since 1992.

“Perhaps the answer to the PSA controversy is already staring us in the face.”

At the same time, practice guidelines cite unproven benefits of PSA screening, as well as the known side effects, which largely reflect the high risks of overdiagnosis and overtreatment that screening engenders.

This issue of NEJM reports two large studies:

The first trial reported no mortality benefit from combined screening with PSA and digital rectal examination (DRE) during a median follow-up of 10 years.

The second trial reported that PSA screening without DRE, at a median follow-up of 9 years, was associated with an absolute reduction of about 7 PC deaths per 10 000 men screened.

Where do we stand?

Serial PSA screening has, at best, a modest effect of PC mortality during the first decade of follow-up. This benefit comes at the cost of substantial overdiagnosis and overtreatment.

“It is important to remember that the key question is not whether PSA screening is effective, but whether it does more good than harm.”

Compared with breast cancer screening, which also has modest effectiveness, PSA screening leads to a much higher risk of overdiagnosis and overtreatment.

“The implications of the trade-offs reflected in these data, like beauty, will be in the eye of the beholder.” “Further analysis will be needed from these trials, as well as from others, if the PSA controversy is to sleep the big sleep.”

A shared decision-making approach to PSA screening, as recommended by most guidelines, seems more appropriate than ever.
The editorialist seems unenthusiastic about screening with PSA. He may be leaning toward DRE. But, why are PC deaths down over the past 17 years?

The bloom has been coming off PSA. We have progressed from enthusiasm, to concern, to doubt.

The articles give a rough guide to help the patients to make a shared-decision about screening:

- If you are asymptomatic, PSA screening will reduce your chances of dying from PC to 1 in 1000 over the next 10 years.
- Screening will increase your chances of receiving a biopsy by 4 in 10.
- It will increase your chances of receiving a radical prostatectomy to 3 in 100.
- Radical therapy will reduce your chances of death from PC in the next 10 years by about 1 in 50.
- Serious adverse effects follow radical surgery.

SCREENING TEST FOR COGNITION

_A Positive And Valid Screening Test For The Detection Of AD_

6-11 SELF ADMINISTERED COGNITIVE SCREENING TEST (TYM) FOR DETECTION OF ALZHEIMER'S DISEASE  {See ALZHEIMER'S DISEASE.}

SMOKING

1-9 CDC PANEL RECOMMENDS PNEUMONIA VACCINE FOR SMOKERS.

The CDC Advisory Committee on Immunizations advises: “All smokers (age 19-64) should receive the 23-valent pneumococcal vaccine.” This is the first time smokers have been targeted for vaccination.

Smokers are at increased risk of developing pneumococcal disease. More than half of adults with pneumococcal disease are current or former smokers.

Smoking can cause structural changes in the respiratory tract that may make individuals more vulnerable to respiratory infections (bacterial and viral). It can also dampen immune response systemically and locally within the lungs. _S pneumoniae_ may adhere more readily to the epithelial cells of smokers.

There is evidence that cessation can reduce risk of respiratory infections.

All individuals over age 65, as well as those with asthma and COPD, should receive the vaccine. Many smokers may have been covered by previous recommendations.
Each Year, 433 000 Premature Deaths; 5 Million Years Of Productive Life Lost; $200 Billion Productivity Losses + Health Care Expenditures

2-7 SMOKING ATTRIBUTABLE MORTALITY, YEARS OF POTENTIAL LIFE LOST, AND PRODUCTIVITY LOSSES—UNITED STATES, 2000-2004

This update is based on data from the CDC’s Smoking Attributable Mortality, Morbidity, and Economic Costs (SAMMEC) system, which estimates smoking-attributable mortality (SAM) and years of productive life lost (YPLL).

Each year, during 2000-2004, cigarette smoking and exposure to tobacco smoke (second hand smoke) resulted in at least 433 000 premature deaths, approximately 5 million YPLL, and $200 billion productivity + health care expenditures.

The three leading specific causes of smoking-attributable death:

- Annually
  - Lung cancer: 129 000
  - Ischemic heart disease: 126 000
  - COPD: 93 000

Leading causes of death, such as lung cancer and COPD could become relatively uncommon in future generations if the prevalence of smoking was substantially reduced.

This is not news to primary care clinicians. I abstracted the report as a preface to the following article.

Financial Incentives Increased Cessation

2-8 A RANDOMIZED, CONTROLLED TRIAL OF FINANCIAL INCENTIVES FOR SMOKING CESSATION

Work sites offer a promising venue for encouraging smoking cessation. Employers are likely to bear many of the excess burdens related to smoking—absenteeism and health-care costs.

This study tested the effectiveness of a financial incentive in improving long-term cessation.

In 2005-06, recruited 878 employee-smokers (mean age 45; 65% male) of a large company at worksites throughout the USA. Most smoked a pack a day. A few smoked two packs. Mean number of previous attempts to quit = 6. One third were considered highly dependent.
All received information about smoking cessation programs. They were encouraged to participate in a program, but were not required to do so.

Randomized to:
1) Financial incentives to stop (n = 436)
2) No financial incentives (n = 442)

The financial incentives:
- $100 for completion of a community-based smoking-cessation program.
- $250 for cessation within 6 months of study enrollment.
- $400 for cessation for 12 months. (Total $750 at one year after randomization.)

Members of the incentive group had higher cessation rates than members of the control group:

<table>
<thead>
<tr>
<th></th>
<th>Control (no incentive)</th>
<th>Incentive group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cessation at 6 months</td>
<td>12% (n = 52)</td>
<td>21% (n = 91)</td>
</tr>
<tr>
<td>Continued abstinence at 12 months</td>
<td>5% (n = 22)</td>
<td>15% (n = 64)</td>
</tr>
<tr>
<td>Continued abstinence at 18 months</td>
<td>4% (n = 16)</td>
<td>9% (n = 41)</td>
</tr>
</tbody>
</table>

To date, financial incentives within health care settings have been directed primarily toward providers through Pay for Performance programs. Given that up to 40% of premature deaths are due to unhealthy behaviors (smoking, poor diet, and sedentary lifestyle) incentives directed toward patients rather than providers may have greater potential for changing behaviors.

Conclusion: Smoking-cessation among company employees who were given both information about cessation programs and financial incentives to quit was higher than among employees who were given program information but no financial incentives.

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I wonder how many will still be abstinent in 5 years.

On a population basis, these results would be impressive. Reducing prevalence of smoking by 5% is a major achievement.

It is interesting that $750 is more of an incentive for some people to quit than the probability of living 10 years longer and feeling 10 years younger.

Financial payment to improve life-styles is not applicable to most persons in the USA. Higher costs for health and life insurance for persons who smoke and those with obesity may influence some to improve their lifestyles. Preference in hiring may also help.
A Higher Sodium/Potassium Excretion Ratio Was Associated With Increased Risk Of CVD.

1-1  JOINT EFFECTS OF SODIUM AND POTASSIUM INTAKE ON SUBSEQUENT CARDIOVASCULAR DISEASE: The Trials of Hypertension Prevention Follow-up Study (TOHP)
[See CARDIOVASCULAR DISEASE]

STROKE

*Style Behaviors Lower Risk Of Stroke.*

3-5  COMBINED EFFECT OF HEALTH BEHAVIORS AND RISK OF FIRST EVER STROKE IN 20 040 MEN AND WOMEN OVER 11 YEARS’ FOLLOW-UP

This study examined the potential magnitude of combined lifestyle behaviors on the incidence of stroke in men and women age 40-79 over a 12 year period.

Created a health behavior score: Points

Non-smoker 1
Physical activity or non-sedentary occupation 1
Alcohol 1 to 14 drinks per week 1
Fruit and vegetable intake 5 or more/day 1

Total score ranging from 0 to 4. (Highest score the healthiest.)

Determined incident cases of stroke

Incidence of stroke decreased in a linear fashion with every point increase in score.

Absolute risks for incident stroke (%)

<table>
<thead>
<tr>
<th>Behavior score</th>
<th>Absolute risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>5.8</td>
</tr>
<tr>
<td>1</td>
<td>6.1</td>
</tr>
<tr>
<td>2</td>
<td>4.0</td>
</tr>
<tr>
<td>3</td>
<td>2.4</td>
</tr>
<tr>
<td>4</td>
<td>1.7</td>
</tr>
</tbody>
</table>

Conclusion: Relatively modest and achievable health behaviors in combination (non-smoking, physically active, moderate alcohol intake, and eating fruits and vegetables) can produce a substantial reduction in risk of stroke.

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Favorable lifestyle behaviors reduce risk of hypertension, diabetes, and coronary heart disease, as well as stroke.
Leading patients to adopt healthy lifestyles is an opportunity and challenge for primary care. If we could get the general population of the US to adopt a healthy lifestyle, I believe our problems with financing good health care for all would disappear.

Getting one patient to stop smoking might be equivalent to avoiding one coronary by-pass.

TEST YOUR MEMORY

A Positive And Valid Screening Test For The Detection Of AD

6-11 SELF ADMINISTERED COGNITIVE SCREENING TEST (TYM) FOR DETECTION OF ALZHEIMER’S DISEASE  {See ALZHEIMER’S DISEASE.]

URINARY INCONTINENCE

Weight Reduction Was Associated With A Decrease In Incontinence

1-4 WEIGHT LOSS TO TREAT URINARY INCONTINENCE IN OVERWEIGHT AND OBESE WOMEN

Obesity is an established and modifiable risk factor for urinary incontinence (UI). Conclusive evidence for a beneficial effect of weight loss is lacking.

This study asked if a behavioral weight–reduction intervention would reduce incontinence.

A randomized trial of overweight and obese women assigned: 1) patients (n = 220) to an intensive six-month weight-loss program (diet, exercise, and behavioral modification), or 2) to a structured education program (n = 112).

All had at least 10 UI episodes per day.

Participants were given a reduced-calorie diet (1200 to 1500 kcal) providing no more than 30% of calories from fat. They were encouraged to gradually increase exercise (brisk walking) to at least 200 minutes a week.

Baseline (means and %): Age 53; BMI 36; postmenopausal 56%; 24-h involuntary urine loss 33g; urge predominant 32%; stress predominant 17%; mixed 33%

<table>
<thead>
<tr>
<th></th>
<th>At 6 months (% change)</th>
<th>Weight-loss group</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>-8</td>
<td>-2</td>
<td></td>
</tr>
<tr>
<td>UI</td>
<td>-47</td>
<td>-28</td>
<td></td>
</tr>
<tr>
<td>Stress incontinence</td>
<td>-58</td>
<td>-33</td>
<td></td>
</tr>
<tr>
<td>Urge incontinence</td>
<td>-42</td>
<td>-26</td>
<td></td>
</tr>
</tbody>
</table>

(Overall, more women with stress incontinence improved that those with urge incontinence.)
A higher number of women in the weight-loss group had a reduction of at least 70% in total number of incontinence episodes per week. (41% vs 22%). A few had 100% reduction (7% vs 4%).

Conclusion: A 6-month behavioral weight loss intervention reduced the frequency of self-reported UI episodes among overweight and obese women.

I congratulate these patients for losing 8% of body weight in 6 months. It will be interesting to know if they maintained weight loss and if their incontinence remained less frequent over then next few years. I believe primary care clinicians can, with assurance, advise obese patients that reduction in UI is another benefit of weight loss.

VASCULAR DISEASE

_Vascular Disease Should Be Used for Secondary Prevention. Use for Primary Prevention Is Debatable._

5-3 ASPIRIN IN THE PRIMARY AND SECONDARY PREVENTION OF VASCULAR DISEASE [See Aspirin]

_The Current Evidence Is Insufficient To Rule Out A Small Yet Important Benefit_

5-4 ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE [See Aspirin]

VITAMIN D

2-1 ASSOCIATION BETWEEN SERUM 25-HYDROXYVITAMIN D LEVEL AND UPPER RESPIRATORY TRACT INFECTION: The Third National Health and Nutrition Examination Survey

Prevention of colds/influenza and “immune boosting” remain the top reasons that Americans take vitamins and herbal supplements.

For decades, vitamin C has been marketed and used for prevention and treatment. Convincing evidence of efficacy in community populations is lacking.

The importance of vitamin D in general health has expanded far beyond rickets. It is involved in the regulation of 1000 human genes. It seems to have promise in the prevention of infection, including upper respiratory tract infections. (**URTI**)

Vitamin D plays an important role in innate immunity.
Respiratory tract infections have been strongly linked epidemiologically with rickets. Although 25(OH)D serum levels of 10 ng/mL prevent rickets, at least 30 ng/dL are advantageous for good health. Approximately 40 ng/mL is considered optimal.

This study examined the association between serum 25(OH)D levels and URTI in a large cross sectional sample representative of the entire US population. The hypothesis was that URTI are inversely related to 25(OH)D levels.

The Third National Health and Nutrition Examination Survey was conducted in 1988-1994. This secondary analysis examined the association between 25(OH)D and recent URTI in over 18 000 participants over age 12. All had serum levels of 25(OH)D determined at baseline.

Participants were asked if they had a cold or cough in the past few days.

RESULTS

<table>
<thead>
<tr>
<th>Serum 25(OH)D</th>
<th>Number</th>
<th>%</th>
<th>Recent URI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10</td>
<td>684</td>
<td>2</td>
<td>24</td>
</tr>
<tr>
<td>10-&lt;30</td>
<td>12 302</td>
<td>53</td>
<td>20</td>
</tr>
<tr>
<td>30 and above</td>
<td>5897</td>
<td>45</td>
<td>17</td>
</tr>
</tbody>
</table>

Participants with levels < 10 had 55% higher odds of a recent URTI, and those with levels 10-30 had 27% higher odds of a recent URTI compared with those whose level was 30 and above.

“The association seems to be robust, with a clinically and statistically significant association present in all seasons, and when controlled for potential confounders.” The association seemed to be stronger in individuals with asthma and COPD.

Current recommendations for D supplementation (200-600 IU daily) are unlikely to achieve optimal serum levels. Supplementation with 1000 IU or more daily, particularly in the winter at higher latitudes, may be required.

Conclusion: Serum 25(OH)D levels had an independent inverse association with recent URTI. Adequate supplementation may reduce incidence of URTIs.

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I would not be surprised to read about a beneficial effect of vitamin D on incidence of pneumonia. Administration to patients with asthma and COPD may be especially beneficial.

The Vitamin D story has been astounding. Diverse conditions related to deficiency, and improved by supplementation seem to be reported each month. How many of these will remain in the next 5 years?

Primary care clinicians now frequently order serum levels and prescribe high doses for those who are deficient. Administration to patients with asthma and COPD may be especially beneficial.
The association of vitamin C with URTI was debated for years without a firm conclusion. It is ironic that the real association was just next door.

Most over-the-counter and prescription vitamin D preparations are in the form of D3, which unit for unit raises serum levels much higher than D2.

Fortunately, vitamin D3 is available without a prescription. Its benefit/harm-cost ratio must be one of the highest for any drug. I would take at least 1000 IU daily.

A Need For Consideration Of Vitamin D Status And Supplementation In Critically Ill Patients

4-6 VITAMIN D DEFICIENCY IN CRITICALLY ILL PATIENTS

Of the 1100 patients in their ICU, 17% had undetectable vitamin D levels.

This prospective study of vitamin D status was conducted in 42 patients referred from ICU to a Department of Endocrinology in Australia.

The investigators classified serum levels of 25(OH)D in ng/mL:

- Sufficient: > 24
- Insufficient: 24 to 12
- Deficient: <12 to 6
- Undetectable: <6

Of the 1100 patients in their ICU, 17% had undetectable vitamin D levels. Among the 42 referred patients, prevalence of hypovitaminosis D was high—the mean serum level of 25(OH)D was 16 ng/mL. Three patients died of neoplastic disease. All 3 had undetectable serum levels of D.

Mean acute physiology scores (APS) and predicted mortality rates in 42 patients:

<table>
<thead>
<tr>
<th>D level</th>
<th>APS</th>
<th>Predicted mortality rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>34</td>
<td>16</td>
</tr>
<tr>
<td>Insufficient</td>
<td>45</td>
<td>35</td>
</tr>
<tr>
<td>Deficient</td>
<td>51</td>
<td>45</td>
</tr>
</tbody>
</table>

Vitamin D deficiency is associated with increased mortality.

Conclusion: “These findings highlight the need for consideration of vitamin D status and supplementation in patients in the ICU.”

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Vitamin D deficiency seems to have become a scourge. And repletion a panacea.

What a remarkable turn of events!

Look for more studies. Meanwhile, I see no harm in repletion in acutely ill patients, as well as in many others.
Vitamin D Insufficiency May Be A Significant Contributor To Neuropathic Pain In Type-2 Diabetes.

4-7 VITAMIN D AS AN ANALGESIC FOR PATIENTS WITH TYPE-2 DIABETES AND NEUROPATHIC PAIN

Hypovitaminosis D is highly prevalent in patients with type-2 diabetes (DM-2). Its impact on neuropathic pain has not been previously evaluated.

This prospective study included fifty-one patients (mean age 62) with DM-2. All had neuropathic pain (burning, tingling, numbness, and throbbing sensations), and reduced sensation to touch.

Measured serum 25(OH)D. All were D insufficient (< 24 ng/mL) Treated all with D3 tablets daily (mean dose = 2059 IU). Reevaluated patients at 3 months.

All patients were D insufficient (mean serum concentration = 18 ng/mL)

At baseline, mean score on a visual analogue pain (VAS) scale (range from 0 to 6) was 3.3—“distressing”. Score on the McGill pain questionnaire was 32.

At 3 months, serum 25D concentrations increased from 18 to 30 ng/mL.

Vitamin D repletion resulted in a statistically significant reduction in pain scores. VAS score improved at 3 months to 1.7; McGill score improved to 19.

There is evidence that vitamin D is neurotrophic and modulates neuromuscular function, and neuronal growth and differentiation. Insufficiency may worsen diabetic nerve damage.

The definition of vitamin D deficiency is an ongoing debate. It is generally defined as serum 25(OH)D concentrations less than 20 ng/mL. The mean post-therapy D level in this study was 30 ng/mL. This was correlated with statistically significant pain reduction.

Conclusion: Vitamin D insufficiency is underrecognized, and may be a significant contributor to neuropathic pain in type-2 diabetes.

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This study was little more than anecdotal. It is provocative.

Primary care physicians are frequently measuring vitamin D levels, and treating deficient patients with high doses—often 50,000 IU every week. At this dose it is non-toxic. Indeed, vitamin D may have one of the highest benefit/harm-cost ratios of any drug. I recently purchased D3 tablets 1000 IU for 3 cents each.

The association of D insufficiency related to DM-2 neuropathy should be tested by primary care physicians to determine clinically significant improvement. I doubt any drug company would launch a study. There would be little profit.
WHOOPING COUGH

6-9 WHOOPING COUGH: *Easily Missed*

Whooping cough (WC), caused by *Bordetella pertussis*, should be considered in any adolescent or adult with an acute cough lasting more than 2 weeks, even if the patient has been immunized. The cough may be the only symptom.

A single raised titer of an IgG antibody to pertussis toxin in oral fluid is validated. It is quick and easy to use in primary care. It is 99% specific.

How is it managed? WC is a notifyable disease. Erythromycin within 3 weeks of onset of symptoms reduces the period of infectivity and may prevent transmission to family members, even though treatment may not affect outcome for the patient. A seven-day course is sufficient.

Prophylaxis with erythromycin should be offered to everyone in households with a vulnerable infant. The illness in infants may be severe and require prompt referral.