PRACTICAL POINTERS FOR PRIMARY CARE

INDEX

JULY – DECEMBER 2006

PRACTICAL CLINICAL POINTS

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO THE FULL ABSTRACTS

JAMA, NEJM LANCET, BMJ

ARCHIVES INTERNAL MEDICINE,

ANNALS INTERNAL MEDICINE

www.practicalpointers.org

PUBLISHED BY PRACTICAL POINTERS, INC.

EDITED BY RICHARD T. JAMES JR., M.D.

400 AVINGER LANE #203

DAVIDSON NC 28036 USA

This index is a reference document based on articles abstracted from 6 flagship journals July-December 2006. It provides a means of recalling to memory, in an evening or two, what the editor considered new and important for primary care.

The numbers in the brackets refer to the full abstract. For example, [7-12] refers to the twelfth article abstracted in July 2006.

It consists of 4 parts:

1) "Practical Clinical Points": This provides an instant reminder of points of clinical interest and importance which primary care clinicians should advise patients about, consider, and be aware of. Links are supplied to the "Highlights of Abstracts and *Editorial Comments*" section.
2) "Medical Subject Headings" (MeSH): A list of 119 medical subject headings from aortic abdominal aneurysm to waist circumference arranged and linked alphabetically to the "Highlights and *Editorial Comments*" section.
3) "Highlights of Abstracts and *Editorial Comments*" section: linked alphabetically to each MeSH. (There may be several articles listed under a MeSH.) The highlights contain a condensation of each abstract. The *Editorial Comments* are those of the editor alone, based on his years-long experience as a practicing primary care internist and as editor and publisher of *Practical Pointers for Primary Care.*
4) The abstract itself provides more detailed information, and the citation.

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

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

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

PRACTICAL CLINICAL POINTS JULY – DECEMBER 2006

Advise:

- **A low glycemic load diet as an important addition to the Mediterranean Diet to reduce risk of CHD [11-4]**
- **Adding nuts to the Mediterranean diet [7-3]**
- **Lifestyle interventions to prevent development of diabetes [11-3]**
- **Flu immunizations for staffs of retirement homes to lower risk of flu in residents [12-1]**
- **Flu immunizations for schoolchildren to lower risk in families [12-3]**
- **Shingles vaccine for all adults over age 50 who have not had herpes zoster [7-2]**

Consider:

- **Treating aortic abdominal aneurysms with ACE-inhibitor [8-5]**
- **More liberal administration of opiates to patients with abdominal pain while awaiting diagnosis [10-5]**
- **Use of ferritin levels to diagnose iron deficiency anemia [10-6]**
- **Use of a "delayed prescription" for patients with acute conjunctivitis [10-7]**
- **This algorithm to manage hyperglycemia in type 2 diabetes [12-4]**
- **Use of supplemental calcium and vitamin D in patients using proton-pump inhibitors long-term [12-8]**
- **Use of statin drugs in patients with chronic heart failure [11-1]**
- **Use of waist circumference to assess risk of obesity [9-2]**
- **Use of an alpha blocker &/or a calcium blocker to aid passage of a low lying ureteral stone [9-3]**
- **The advantages for continuing alendronate for 10 years to treat osteoporosis [12-7]**
- **Combined acetylcholine blocker + alpha adrenergic blocker to treat symptoms of overactive bladder [11-10]**

Be aware of:

- **The staying power of the Polypill" concept, and possible use in patients with diabetes [7-8]**
- **Risk of acetaminophen in patients with liver disease, or at risk for liver disease [12-0]**
- **The possibility that your patients may be medically illiterate. He requires special attention 7-1]**
- **Checking HbA1c level in your patients with diabetes more often than several times a year may be misleading [9-5]**
- **There comes a time to stop PSA screening in men with limited life expectancy [11-2]**
- **More experience is required to determine the benefit/harm-cost of incretin enhancers for type 2 diabetes. [12-5]**
- **More experience is required to determine the benefit/harm-cost of inhaled insulin. [12-6]**
- **More experience is required to determine the benefit/harm-cost of varenicline to aid smoking cessation [7-5]**

MEDICAL SUBJECT HEADINGS (MESH) JULY–DECEMBER 2006

HIGHLIGHTS AND *EDITORIAL COMMENTS* JANUARY –JUNE 2006

ABDOMINAL AORTIC ANEURYSM

Associated With Reduced Risk Of Rupture Of AAA

8-10 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND AORTIC RUPTURE

Angiotensin II is strongly upregulated in human aortic aneurysms with increases mediated through pathways dependent on angiotensin converting enzyme. Animal studies suggest that ACE-inhibitors (**ACE-i**) might slow the progression of AAA and prevent expansion and rupture. Such protection was not apparent for angiotensin II blockers, calcium blockers, or hydralazine. This suggests that the mechanism involved might *not* be related to lowering of BP.

Retrospective, population-based, case-control study included consecutive patients older than age 65 (n = over 15 000; the majority men; mean age = 75) admitted to hospitals in Ontario between 1992 and 2002. All had a primary diagnosis of AAA. About ¼ were ruptured; ¾ were intact.

Cases = individuals with ruptured AAA. Controls = remaining individuals with unruptured AAA.

Compared use of ACE-i in both groups (primarily lisinopril, enalapril, and ramipril), defined as two or more prescriptions in the year before, with at least one prescription in the 3 months immediately preceding admission.

Patients who had received ACE-i before admission were less likely to present with rupture. (Odds ratio = 0.82.)

Rupture:	Taking ACE-i (n = 665)	Not taking ACE-i (n = 2761)
	133 (20%)	635 (23%)

(Difference = 3% NNT to prevent one rupture = 33.)

No protective associations were evident for beta-blockers, calcium blockers, alpha blockers, or thiazides,

Conclusion: ACE-i were associated with reduced risk of rupture of AAA, unlike other antihypertension agents.

ACE-i are favored first line drugs for treatment of hypertension. This may be an added attraction. Pharmacokinetic properties of ACE-I and angiotensin II blockers are similar, but they are not identical.

Remember smoking is strongly associated with risk of AAA.

ACE-i are remarkable drugs, related to improvement in prognosis of many cardiovascular events. This is another example.

ABDOMINAL PAIN

This May Save The Patient Hours Of Pain.

10-5 DO OPIATES AFFECT THE CLINICAL EVALUATION OF PATIENTS WITH ACUTE ABDOMINAL PAIN?

Clinicians have traditionally withheld opiate analgesia from patients with acute abdominal pain until after evaluation by a surgeon. This is out of concern that analgesia may alter the physical findings, and interfere with

diagnosis. Older textbooks of surgery historically discouraged opiate analgesia for patients with acute abdominal pain.

This systematic review included 12 placebo-controlled randomized trials of opioid analgesia (3 in children and 9 in adults). All reported changes in the history, physical examination, or diagnostic errors resulting in "management errors" due to opiate administration. Management errors were defined as performance of unnecessary surgery, or failure to perform necessary surgery in a timely fashion.

Changes in physical examination: Studies showed trends toward increased risks of altered findings on the abdominal examination due to opiate administration. Relative risk of altered findings (opiates vs placebo) = 1.51. (95% confidence interval (CI) = +0.85 to +2.69)

Management errors as a marker for important changes in the physical examination: Opiates had no significant association with management errors. (RR = +0.3% absolute increase; (CI = -4.1% to + 4.7%). ["The magnitude of this nonsignificant increase in incorrect decisions is very small. If it had been significant, 333 patients would need to receive opiates to result in one management error attributed to the analgesia." "These data are also compatible with fewer management errors among patients receiving opiates." Across all trials, with adequate analgesia, opiate administration may be associated with a non-significant absolute *decrease* in risk of management errors.

The evidence suggests that administration of opiates does not substantially alter the history of the illness.

"Given the humane duty of physicians to relieve pain and the totality of the available evidence, clinicians should administer analgesia unless further studies document adverse events directly attributable to opiates."

ACETAMINOPHEN

"Might Be Associated With Exaggerated Liver Injury In Some Individuals."

12-9 PARACETAMOL (ACETAMINOPHEN; *TYLENOL*); *Are Therapeutic Doses Entirely Safe?*

Acetaminophen (eg, *Tylenol*) is thought to be safe in recommended doses (up to 4 grams daily in adults). It is currently the most widely used analgesia and antipyretic drug worldwide.

It is hepatotoxic and nephrotoxic at doses greater than 4 g a day. It has become an important cause of acute liver failure. The most severe cases may require liver transplant. Mortality may be high.

In recent years, unintended overdoses, rather than those that are intentional, have been the main cause of acetaminophen-induced acute liver failure in the USA. The dose leading to liver failure may be as low as 7 grams a day.

A recent study was designed to determine why abnormal liver function tests were observed during studies of clinical development of a new combination of an opioid (hydrocodone) and acetaminophen. Participants were randomly assigned to placebo, acetaminophen-alone 4 g a day, or a combination of 4 g acetaminophen with one of three opioids. Duration of observation = 14 days. Although trough acetaminophen concentrations did not exceed therapeutic limits in any group, up to 44% of participants in the acetaminophen groups (including those given acetaminophen alone) had concentrations of alanine aminotransferase (ALT) more than three times the upper limit of normal (suggesting liver injury). No participant given placebo had an increase to this level. In

27% of participants ALT levels were increased to more than 8 times normal. The investigators concluded that the acetaminophen content was associated with ALT elevations.

Concomitant administration of opioids did not seem to increase ALT levels.

Awareness of possible toxicity is particularly important for people who are likely to be at high risk for hepatotoxicity—those dependent on alcohol, chronic users of acetaminophen, the severely malnourished, smokers, and those with acute liver disease.

I believe this is a valid clinical point. Primary care clinicians should be alert to possible acetaminophen toxicity. Note the rapid development of transferase elevations (within 14 days). I wonder—Why, considering the vast usage of acetaminophen, has this toxicity not been reported and disseminated before? My Goodman and Gilman "Pharmacological Basis of Therapeutics" does not mention liver toxicity from usual doses of acetaminophen, only from excessive doses.

Prevalence of impaired liver function is high in the US. This includes many elderly persons otherwise in good health..

The prevalence of non-alcoholic steatosis and steatohepatitis is increasing with the obesity epidemic. Are these patients more susceptible to toxic effects of acetaminophen?

ACUTE CONJUNCTIVITIS (See CONJUNCTIVITIS)
ADHERENCE TO DRUG THERAPY (See DRUG THERAPY)

ALCOHOL

Is A Glass Of Wine With Dinner Part Of A Healthy Lifestyle?

10-7 ALCOHOL CONSUMPTION AND RISK FOR CORONARY HEART DISEASE IN MEN WITH HEALTHY LIFESTYLES.

This study considered the effect of long-term moderate alcohol consumption on incidence of MI in over 8800 men who consistently reported healthy lifestyles. (Ie, alcohol in addition to the healthy lifestyle.) All reported 4 healthy lifestyle behaviors: 1) body mass index less than 25, 2) moderate to vigorous activity for 30 minutes or more daily, 3) not smoking, and 4) a high intake of vegetables, fruits, cereal fiber, fish, chicken, nuts, soy, and polyunsaturated fat. And, low consumption of trans fat, and red and processed meats.

Over 16 years of follow-up, determined incidence of non-fatal MI, and fatal coronary heart disease according

to reported average daily intake of beer, wine, and liquor.

Hazard ratios for MI (multivariate adjusted) of average daily intake of alcohol (g per day) compared with abstention:

0	0.1 to 4.9	5.0 to 14.9	15 to 29.0	30 and over.
1.00	0.92	0.52	0.32	0.70

(In absolute numbers, the differences between groups were small.)

In this prospective analysis of men with healthy lifestyles, moderate alcohol consumption was associated with a lower risk for MI, with the lowest risk in men who drank an average of 5 to 30 g/d (approximately one half to 2 drinks).

The individual and societal complications of heavy drinking are well known. "It is easy to understand why clinical guidelines encourage physicians and patients to concentrate on seemingly more innocuous interventions."

Because of the risks associated with high alcohol intake, clinical guidelines do not recommend alcohol consumption. We have other safer and proven interventions to lower risk of cardiovascular disease. However, healthy behaviors are not mutually exclusive. Pursuit of exercise does not obviate the need for a healthy diet and smoking cessation.

Conclusion: In men with healthy lifestyles, already at low risk for MI, moderate alcohol intake was associated with lower risk for MI.

The apparently protective effect of moderate alcohol intake has been a frequent observation noted in the primary care literature. The evidence has been epidemiological, but consistent. Some epidemiologists even suggest that abstinence is a risk factor. Confounding factors cannot be excluded.

What should the primary care clinician advise? Other lifestyle factors certainly take priority.

For people who already drink, I believe we may advise that a glass of wine with dinner, may be slightly protective. Most clinicians would not prescribe it as the sole factor to reduce risk. I would not prescribe it de-novo. The other lifestyle factors, especially smoking, are more important.

ALENDRONATE (See OSTEOPOROSIS)

ALZHEIMER'S DISEASE

"A Limited, But Sometimes Necessary Role"

10-8 EFFECTIVENESS OF ATYPICAL ANTIPSYCHOTIC DRUGS IN PATIENTS WITH ALZHEIMER'S DISEASE

Psychotic symptoms affect more than half of patients with Alzheimer's disease (**AD**). Second generation (atypical) antipsychotic drugs are widely used in treatment.

This trial followed over 400 patients (mean age 78) with AD. All were ambulatory and living at home or in an assisted-living facility. All had delusions, hallucinations, aggression, or agitation. Symptoms were severe enough to disrupt functioning.

Patients were randomized to: 1) olanzapine (*Zyprexa*); 2) risperidone (*Risperidal*), or 3) placebo.

Eighty two % of patients discontinued the initially assigned medication during the 36-week follow-up; 18% continued.

Discontinued assigned treatment due to intolerability: olanzapine 24%; risperidone 18%; placebo 8%.

At least minimal improvement in Clinical Global Impression of Change scale at 12 weeks: olanzapine 32%; risperidone 29%; placebo 21%. (Not statistically significant.)

Both olanzapine and risperidone were equally effective and were superior to placebo in treating behavioral problems. The benefit was limited to a subgroup of patients who tolerated the drugs.

Flexible dosing (as used in this study) ensures one of the core principles of geriatric pharmacology "Start low and go slow, but go". Clinicians should start a drug at a dose at the lower end of the plausible therapeutic index and then increase the dose until there is efficacy or intolerable side effects

Conclusion: These results suggest that these drugs have a limited, but sometimes necessary role in the care of patients with AD. Although the atypical antipsychotic drugs were more efficacious than placebo, adverse effects limited their overall effectiveness.

The FDA label for antipsychotic medications states they are not approved for treatment of dementia-related psychosis. They display a "black box" warning—"Elderly patients with dementia-related psychosis are at increased risk of death compared with placebo."

What should the primary care clinician do? I believe many primary care clinicians who care for difficult AD patients will prescribe these drugs despite the FDA warning, realizing that many patients will not tolerate the drug. Careful assessment of individual response is a key. Care to treat the patient first, and not to primarily benefit the caregiver or nursing staff.

Note that about 20% of patients in the trial responded and were able to continue the drug. The authors do not state that these drugs should not be used, only that they may not benefit and may be associated with adverse effects which precludes their continuation.

I believe the core principles of geriatric pharmacology "Start low and go slow" applies to almost all drugs used long-term.

ANEMIA

"The Ferritin Assay Provides A Simple Method Of Discriminating Between Iron Deficiency And Anemia Of Chronic Inflammation"

10-6 INVESTIGATING IRON STATUS IN MICROCYTIC ANEMIA

To diagnose iron deficiency, measurement of ferritin is superior to iron and iron binding capacity or transferrin saturation. Elderly patients with anemia require a ferritin assay in order to establish whether iron deficiency is present.

Ferritin greater than 100 ug/L rules out iron deficiency. Under 15 ug/L rules in iron deficiency. The probability of iron deficiency remains high until the ferritin level is greater than 40 for the general population, and greater than 70 for those with chronic inflammation or liver disease.

MCV over 95 fL rules out iron deficiency. A low MCV (less than 85 fL) does not prove iron deficiency (especially in the elderly and those with inflammatory diseases). In anemic patients, the probability of iron deficiency increases with decreasing MCV, but no specific cut-off value can be used. About 20% of elderly patients with a MCV of under 75 fL will *not* have iron deficiency. They will most likely have the anemia of chronic inflammation. "Microcytic anemia alone is not sufficient to diagnose iron deficiency."

Ten clinical points. Read the full abstract.

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

"Angiotensin-Converting Enzyme Inhibitors Have The Broadest Effect Of Any Drug In Cardiovascular Medicine"

8-4 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN STABLE VASCULAR DISEASE WITHOUT LEFT VENTRICULAR SYSTOLIC DYSFUNCTION OR HEART FAILURE. ***A Combined Analysis of Three Trials.***

This study computed cardiovascular outcomes and total mortality reported by 3 large studies of over 29 000 patients with established vascular disease, but without HF or left ventricular systolic dysfunction. The studies compared three different ACE-i: perindopril, trandolapril, and ramipril, with placebo.

All subjects had a history of cardiovascular disease: previous myocardial infarction (MI), stroke or ischemic attack, coronary bypass surgery (**CABG),** and peripheral arterial disease. Some had hypertension and diabetes. None had HF or left ventricular systolic dysfunction. (**LVSD**)

Follow-up a mean of 4.5 years.

When the 3 trials were combined	ACE (%)	Placebo (%)
All cause mortality	7.8	8.9
Cardiovascular mortality	4.3	5.2
Non-fatal MI	5.3	6.4
Stroke	2.2	2.8
Heart failure	2.1	2.7
CABG	6.0	6.9
The composite outcome of cardiovascular mortality, non-fatal MI, or stroke:	10.7	12.8

(*The NNT for 4.5 years to prevent one composite outcome = 48*.)

ACE-i reduce serious vascular events in patients with cardiovascular disease who do *not* have evidence of HF or left ventricular systolic dysfunction.

ACE-i are truly remarkable drugs, Unfortunately, many patients cannot tolerate them due to cough. I suspect angiotensin II blockers would offer as great a benefit. They certainly should be tried in the many patients who do not tolerate ACE-i

A similar meta-analysis "Angiotensin-Converting Enzyme Inhibitors in Patients with Coronary Heart Disease and Absence of Heart Failure or Left Ventricular Systolic Dysfunction" appeared in Archives Int Med April 10, 2006; 166: 787-96. (See Practical Pointers April 2006 [4-11]) It reported similar benefits over a period of 4 years in a high risk group.

ACE-i are expensive Ramipril (Altace) 10 mg daily would cost about $3200 for 4 years. This is for a one in 48 chance of a reduction of the composite of death, MI or stroke. Because the stakes are high, many patients would likely accept the drug despite knowing that the likelihood of benefit is small and the cost high.

Associated With Reduced Risk Of Rupture Of AAA

8-10 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND AORTIC RUPTURE

Angiotensin II is strongly upregulated in human aortic aneurysms with increases mediated through pathways dependent on angiotensin converting enzyme. Animal studies suggest that ACE-inhibitors (**ACE-i**) might slow the progression of AAA and prevent expansion and rupture. Such protection was not apparent for angiotensin II blockers, calcium blockers, or hydralazine. This suggests that the mechanism involved might *not* be related to lowering of BP.

Retrospective, population-based, case-control study included consecutive patients older than age 65 (n = over 15 000; the majority men; mean age = 75) admitted to hospitals in Ontario between 1992 and 2002. All had a primary diagnosis of AAA. About ¼ were ruptured; ¾ were intact.

Cases = individuals with ruptured AAA. Controls = remaining individuals with unruptured AAA.

Compared use of ACE-i in both groups (primarily lisinopril, enalapril, and ramipril), defined as two or more prescriptions in the year before, with at least one prescription in the 3 months immediately preceding admission.

Patients who had received ACE-i before admission were less likely to present with rupture. (Odds ratio = 0.82.)

Rupture:	Taking ACE-i (n = 665)	Not taking ACE-i (n = 2761)
	133 (20%)	635 (23%)

(Difference = 3% NNT to prevent one rupture = 33.)

No protective associations were evident for beta-blockers, calcium blockers, alpha blockers, or thiazides,

Conclusion: ACE-i were associated with reduced risk of rupture of AAA, unlike other antihypertension agents.

ACE-i are favored first line drugs for treatment of hypertension. This may be an added attraction. Pharmacokinetic properties of ACE-I and angiotensin II blockers are similar, but they are not identical.

Remember smoking is strongly associated with risk of AAA.

ACE-i are remarkable drugs, related to improvement in prognosis of many cardiovascular events. This is another example.

ANGIOTENSINOGEN-ANGIOTENSIN - ALDOSTERONE SYSTEM

10-11 THE ANGIOTENSINOGEN-ANGIOTENSIN I - ANGIOTENSIN II- ALDOSTERONE SYSTEM

Also Known As the Renin-Angiotensin System

The angiotensinogen-angiotensin I-angiotensin II-aldosterone system (**A-AI-AII-A**) is a basic physiological system which helps maintain homeostasis. The complexity of the system is maddening. *(I prepared this simplified abstract for my own edification and enjoyment. RTJ)*

Inhibition of the system has been termed one of the most effective and important ways to intervene in the pathogenesis of cardiovascular and renal disorders including hypertension, left ventricular systolic dysfunction,

acute myocardial infarction, and chronic renal disease (eg, diabetic). It also reduces risk when given to patients at high risk for cardiovascular disease.

This review includes the A-AI-AII-A cascade, the enzymes facilitating progress of the cascade, and mentions five drugs which block various stages of the cascade. See the full abstract.

AORTIC ANEURYSM (See ABDOMINAL AORTIC ANEURYSM)

APPENDICITIS

"The Diagnosis Is Primarily A Clinical One"

9-6 ACUTE APPENDICITIS: *A Refresher Course of Clinical Points*

Thirteen clinical points. Most old; some new. Read the full abstract.

ATORVASTATIN (See STROKE)

ATYPICAL ANTIPSYCHOTIC DRUGS (See ALZHEIMER'S DISEASE)

BARIATRIC SURGERY (See OBESITY)

BEVACIZUMAB (See MACULAR DEGENERATION)

BLOOD PRESSURE (See HYPERTENSION)

BODY MASS INDEX (See OBESITY)

BUPROPRION (See SMOKING)

CARBOHYDRATE (See DIET)

CARBOHYDRATE SCORE (See DIET)

CARDIOVASCULAR DISEASE

The Healthy Diet Is Not A Low Fat Diet, It Is A Selected Fat Diet.

7-3 EFFECTS OF A MEDITERRANEAN-STYLE DIET ON CARDIOVASCULAR RISK FACTORS

Incidence rates of cardiovascular disease **(CVD)** have marked geographical differences. One factor may be diet. High adherence to the Mediterranean diet **(MD)** is associated with a reduction in mortality. The diet may also be associated with a reduced BP and improved lipid profiles.

Olive oil, a rich source of mono-unsaturated fatty acids is a main component of the MD.

Frequent nut intake has been associated with a decrease in rates of CVD.

This study randomized subjects to one of 3 diets:

1) Low fat diet: Subjects were advised to reduce intake of all types of fat. They were given a leaflet describing the American Heart Association recommendations. Diet was similar to the DASH diet.
2) MD with added olive oil: Participants were given one liter of olive oil to consume each week.
3) MD with added nuts: Participants were given sachets of nuts to take 30 g / day.

Compared with the low fat diet, the 2 MDs produced beneficial changes BP, fasting glucose, insulin levels, and lipids. Not much difference between olive oil and nut groups.

The diets (except for olive oil and nut content) were similar to the DASH diet which is associated with lowering of BP. The authors state that if salt were restricted (as in the low sodium DASH diet) BP would likely be lowered still more.

Compared with a low-fat diet (similar to the DASH diet), a MD supplemented with virgin olive oil or nuts had beneficial effects on cardiovascular risk factors.

I would assume that a combination of olive oil and nuts would produce the same benefits, and would be easier to adhere to. Why not consider other mono-unsaturated oils (peanut; canola) beneficial as well? They may be less expensive than olive oil.

For prevention of CVD, the "low-fat" diet is no longer considered the most beneficial. The most beneficial diet is a moderately high mono-unsaturated fat, very low saturated fat; no trans fat diet.

I believe poly-unsaturated fats may be substituted for mono-unsaturated fats and produce similar benefits. Some would add low-salt and low glycemic load to the diet.

The added nut and olive oil diet would likely increase weight over time. If one adopts these diets, energy intake must not be increased. This may be difficult for individual patients.

For patients and physicians who are interested in a detailed description of the MD go to:

www.postgradmed.com/issues/2002_02/curtis.htm Accessed August 28, 2006

Google also presents a variety of information.

"Angiotensin-Converting Enzyme Inhibitors Have The Broadest Effect Of Any Drug In Cardiovascular Medicine"

8-4 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS IN STABLE VASCULAR DISEASE WITHOUT LEFT VENTRICULAR SYSTOLIC DYSFUNCTION OR HEART FAILURE. ***A Combined Analysis of Three Trials.***

This study computed cardiovascular outcomes and total mortality reported by 3 large studies of over 29 000 patients with established vascular disease, but without HF or left ventricular systolic dysfunction. The studies compared three different ACE-i: perindopril, trandolapril, and ramipril, with placebo.

All subjects had a history of cardiovascular disease: previous myocardial infarction (MI), stroke or ischemic attack, coronary bypass surgery (**CABG),** and peripheral arterial disease. Some had hypertension and diabetes. None had HF or left ventricular systolic dysfunction. (**LVSD**)

Follow-up a mean of 4.5 years.

When the 3 trials were combined	ACE (%)	Placebo (%)
All cause mortality	7.8	8.9
Cardiovascular mortality	4.3	5.2
Non-fatal MI	5.3	6.4
Stroke	2.2	2.8
Heart failure	2.1	2.7
CABG	6.0	6.9

The composite outcome of cardiovascular mortality, non-fatal MI, or stroke:

10.7 12.8

(*The NNT for 4.5 years to prevent one composite outcome = 48*.)

ACE-i reduce serious vascular events in patients with cardiovascular disease who do *not* have evidence of HF or left ventricular systolic dysfunction.

ACE-i are truly remarkable drugs, Unfortunately, many patients cannot tolerate them due to cough. I suspect angiotensin II blockers would offer as great a benefit. They certainly should be tried in the many patients who do not tolerate ACE-i

A similar meta-analysis "Angiotensin-Converting Enzyme Inhibitors in Patients with Coronary Heart Disease and Absence of Heart Failure or Left Ventricular Systolic Dysfunction" appeared in Archives Int Med April 10, 2006; 166: 787-96. (See Practical Pointers April 2006 [4-11]) It reported similar benefits over a period of 4 years in a high risk group.

ACE-i are expensive Ramipril (Altace) 10 mg daily would cost about $3200 for 4 years. This is for a one in 48 chance of a reduction of the composite of death, MI or stroke. Because the stakes are high, many patients would likely accept the drug despite knowing that the likelihood of benefit is small and the cost high.

CARDIOVASCULAR RISK FACTORS (See CARDIOVASCULAR DISEASE)
CARE-HOME STAFF (See INFLUENZA)
CELECOXIB (See COLORECTAL ADENOMAS)
CHOLINESTERASE INHIBITORS (See DEMENTIA)

CHRONIC FATIGUE SYNDROME

"A Distinguishable Subset Within The Broad Diagnostic Category Of Chronic Fatigue Syndrome."

9-9 POST-INFECTIVE AND CHRONIC FATIGUE SYNDROMES PRECIPITATED BY VIRAL AND NON-VIRAL PATHOGENS.

Post-infective fatigue states have been linked to a diverse spectrum of severe infections, although associations between the syndrome and infections are not consistent.

This prospective population-based cohort study delineated the risk factors, symptom patterns, and longitudinal course of prolonged illnesses after a variety of acute infections.

This study, in a rural area of Australia, was based on patients with IgM positive serological results indicating acute Epstein-Barr virus, Q fever, or Ross-River virus infections.

Of the subjects (n = 253; age range 17-63), none had symptoms of the infection for over 6 weeks. None reported pre-existing medical disorders or drug abuse likely to be associated with prolonged fatigue.

Used a self-reported questionnaire assessing 6 symptom domains: acute illness; irritability; fatigue; neurocognitive disturbance; musculoskeletal pain; and mood disturbance.

The case rate for provisional post-infective fatigue syndrome (%):

Six weeks 35

Three months	27
Six months	12
Twelve months	9

Compared with subjects who recovered more promptly (n = 224), the 28 subjects considered to have the post infective fatigue syndrome reported higher scores for the fatigue factor.

Fatigue (of the 6 symptom domains) was the strongest and most consistent correlation with functional impairment ("days out of role in the past month").

The syndrome was predicted largely by the severity of the acute illness, rather than by demographic, psychological, or microbiological factors.

Prolonged fatigue states after infections are common and disabling. They may persist for 12 months or longer.

I abstracted this study because I believe some patients do indeed develop chronic fatigue after a serious infection. These patients deserve recognition and support. I do not think its cause is psychological. I doubt, however, that it lasts for years.

I believe it differs from what we have heretofore termed "The Chronic Fatigue Syndrome". It may likely be differentiated by terming this syndrome "The Post-infection Fatigue Syndrome".

I hope this provocative study will provoke further investigations. The point is clinically important.

COLORECTAL ADENOMAS

Harm Outweighs Benefit

8-8 CELECOXIB FOR THE PREVENTION OF SPORADIC COLORECTAL ADENOMAS

This trial randomized patients who had adenomas removed before study entry to the COX-2 inhibitor celecoxib (*Celebrex*) 200 mg twice daily or 400 mg twice daily for 3 years. Repeat colonoscopies were performed at 1 and 3 years. Compared with placebo, celecoxib reduced rate of recurrent adenomas by about 20%

Adverse events were more common in the celecoxib groups

	Placebo	200 mg	400 mg
Serious cardiovascular events	1%	2.6%	3.4%
Serious cardiovascular events in patients with history of cardiovascular disease at baseline	3%	9%	9%

(Absolute difference = 6%; NNT to harm one patient over 3 years = 17)

Conclusion: "These findings indicate that celecoxib is an effective agent for prevention of colorectal adenomas, but, because of potential cardiovascular events, cannot be routinely recommended for this indication."

I abstracted this study because it raises considerable caution about general use of celecoxib regularly for long periods. Note the usually recommended dose for osteoarthritis is 100 mg twice a day, considerably less than that used in the study.

The benefit / harm cost ratio of celecoxib may be very low because of incidence of serious harms—indeed low enough to contraindicate use of higher doses in primary care. I believe there is also a cardiovascular risk of lower doses (100 mg twice daily)—certainly much greater than aspirin which is actually related to lowering cardiovascular risks.

I would not use celecoxib at any dose in patients with established cardiovascular disease, or indeed any NSAID except possibly naproxen.

Naproxen has been reported to be the safest, at least in regard to risk of atherothrombotic events.

A good rule—use acetaminophen first.

CONGESTIVE HEART FAILURE (SEE HEART FAILURE)

CONJUNCTIVITIS

Another Application of the Delayed Prescription

8-5 MANAGEMENT STRATEGIES FOR ACUTE CONJUNCTIVITIS IN GENERAL PRACTICE:

A pragmatic, open, randomized, controlled trial in 30 general practices compared: 1) immediate antibiotic (chloramphenicol eye drops), 2) delayed antibiotic, or 3) no antibiotic (controls), in over 300 patients with acute infective conjunctivitis.

Use of antibiotic:	Immediate	Delayed	No antibiotic
Actually filled prescriptions	99%	53%	30%
No. (%) who believed antibiotics are very effective	67	55	47

(*Note : Only about half returned to receive a delayed prescription.*)

Delaying antibiotics for conjunctivitis in primary care was associated with similar severity and duration of symptoms and with reduced antibiotic use.

There was no difference between groups in cure rate at day 8. Outcomes in the delayed group and the control group were not significantly different.

The average score of severity of symptoms days 1-3 did not differ significantly between groups. The immediate group was more likely to believe that antibiotics were effective, and were more likely to state they would re-attend for future conjunctivitis. (Ie. were “medicalized”.)

Significant bacterial growth was evident in 50% of swabs taken (69 of 138). No significant difference in outcomes between those positive and negative.

Conclusion; A delayed prescription is likely the most appropriate strategy in primary care.

The effect of the patient’s perception that the antibiotic “cured” the infection leads them to return for the same prescription should the infection recur, or if another infection occurs. (“Medicalization”)

Before giving a delayed prescription, U.S. primary care clinicians would likely individualize and consider the severity of the disease, and the patient’s perceived anxiety and preference. I would give the patient the option to fill the prescription immediately despite my advice that delay may be more appropriate.

I believe most U.S. primary care clinicians, when prescribing a delayed prescription, would give the patient a prescription at the first visit with the admonition not to get it filled unless the condition worsened or was not considerably improved in 2 to 3 days. This would eliminate a return visit.

The investigators, however, stated that requiring a patient to return to the office to receive the delayed prescription may have reduced antibiotic use compared with providing the prescription immediately and advising delay.

Similar investigations have reported that upper respiratory infections, acute bronchitis, and select patients with sore throat fall into the same classification—no benefit from antibiotics, and increasing "medicalization" (patients' belief that the antibiotic actually cured), leading to additional requests for antibiotics should another infection occur.

I believe that patients are not much concerned that overuse of antibiotics will lead to development of bacterial resistance. They would likely be more concerned about adverse reactions to the drug. They should be informed about this possibility.

CORONARY HEART DISEASE

Is A Glass Of Wine With Dinner Part Of A Healthy Lifestyle?

10-7 ALCOHOL CONSUMPTION AND RISK FOR CORONARY HEART DISEASE IN MEN WITH HEALTHY LIFESTYLES.

This study considered the effect of long-term moderate alcohol consumption on incidence of MI in over 8800 men who consistently reported healthy lifestyles. (Ie, alcohol in addition to the healthy lifestyle.) All reported 4 healthy lifestyle behaviors: 1) body mass index less than 25, 2) moderate to vigorous activity for 30 minutes or more daily, 3) not smoking, and 4) a high intake of vegetables, fruits, cereal fiber, fish, chicken, nuts, soy, and polyunsaturated fat. And, low consumption of trans fat, and red and processed meats.

Over 16 years of follow-up, determined incidence of non-fatal MI, and fatal coronary heart disease according
to reported average daily intake of beer, wine, and liquor.

Hazard ratios for MI (multivariate adjusted) of average daily intake of alcohol (g per day) compared with abstention:

0	0.1 to 4.9	5.0 to 14.9	15 to 29.0	30 and over.
1.00	0.92	0.52	0.32	0.70

(In absolute numbers, the differences between groups were small.)

In this prospective analysis of men with healthy lifestyles, moderate alcohol consumption was associated with a lower risk for MI, with the lowest risk in men who drank an average of 5 to 30 g/d (approximately one half to 2 drinks).

The individual and societal complications of heavy drinking are well known. "It is easy to understand why clinical guidelines encourage physicians and patients to concentrate on seemingly more innocuous interventions."

Because of the risks associated with high alcohol intake, clinical guidelines do not recommend alcohol consumption. We have other safer and proven interventions to lower risk of cardiovascular disease. However, healthy behaviors are not mutually exclusive. Pursuit of exercise does not obviate the need for a healthy diet and smoking cessation.

Conclusion: In men with healthy lifestyles, already at low risk for MI, moderate alcohol intake was associated with lower risk for MI.

The apparently protective effect of moderate alcohol intake has been a frequent observation noted in the primary care literature. The evidence has been epidemiological, but consistent. Some epidemiologists even suggest that abstinence is a risk factor. Confounding factors cannot be excluded.

What should the primary care clinician advise? Other lifestyle factors certainly take priority.

For people who already drink, I believe we may advise that a glass of wine with dinner, may be slightly protective. Most clinicians would not prescribe it as the sole factor to reduce risk. I would not prescribe it de-novo. The other lifestyle factors, especially smoking, are more important.

"A Higher Glycemic Load Was Strongly Associated With An Increased Risk Of CHD"

11-4 LOW-CARBOHYDRATE-DIET SCORE AND THE RISK OF CORONARY HEART DISEASE IN WOMEN

This study evaluated data in the Nurses Health Study (> 82 000 women) which permitted comparison of a low carb, higher fat, higher protein diet with a high carb, lower fat, lower protein diet.

All subjects had completed validated food-frequency questionnaires several times during the study.

Divided mean daily intakes of carbohydrate, protein and fat into deciles beginning with the lowest intake of carbs, and progressing to the highest. (*1990 questionnaire data*):

Decile with lowest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1539	37%	40%	23%

Glycemic load

73

Decile with highest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1814	59%	26%	15%

Glycemic load

145

Also determined the % of energy of animal fat and vegetable fat, and animal protein and vegetable protein for

each decile of carb intake:

Over 20 years (over 1 500 000 person-years), documented 1994 new cases of CHD.

On average, body mass index increased from baseline over 20 years by about 2.5 units *regardless* of

the carbohydrate intake.

After controlling for multiple potential confounders, the relative risk (RR) of coronary heart disease between

those in the highest intakes of carbohydrate (lowest fat) vs those in the lowest intake of carbohydrate (highest fat) was 0.94. (No statistically significant difference.) "Total dietary fat has not been associated with a risk of coronary heart disease." *(Ie, in this study, no evidence that diets low in carb and higher in fat and protein were associated with increased risk of CHD.)*

A higher glycemic load was strongly associated with an increased risk of CHD. (RR of highest glycemic load

vs lowest = 1.90 vs 1.00, (*Almost double*)

"We found that, after taking into account confounding variables, a low carbohydrate diet (*higher fat*) was *not*

associated with a risk of coronary heart disease in this large prospective cohort of women."

When vegetable sources of fat were chosen, a low carbohydrate intake was associated with a moderately *lower* risk of CHD than when animal sources of fat were chosen. (RR = 0.70)

Conclusion: Diets lower in carbohydrate and higher in protein and fat were *not* associated with increased risk of CHD in women. When vegetable source of fat and protein were chosen, the RR of CHD was lower than when animal fat and animal protein were chosen. Low glycemic load diets were associated with a lower risk of CHD.

This remarkable study is more complicated than I have indicated. It was difficult to abstract. I believe I have captured the essence of the outcomes.

The study points out that a low glycemic load diet is part of a healthy diet. Higher levels of plasma glucose are a risk factor.

It confirms that a low saturated fat diet is healthier, and that vegetable fats (oils; mono-unsaturated fat) and polyunsaturated fats are also important parts of the healthy diet.

It also confirms how difficult it is to lose weight on any diet, and to maintain the loss.

The healthy diet:

1) Low glycemic load

2) Low saturated fat; high poly- unsaturated fat, and mono-unsaturated fat

3) Zero trans fat

4) Total calories adjusted to maintain BMI under 25

Add a glass of wine before dinner, and this is similar to the Mediterranean diet.

CYSTATIN C

An Emerging, Simple Marker of Kidney Function. Better than Creatinine-based Estimates

8-12 CYSTATIN C, GLOMERULAR FILTRATION RATE, and DECREASED KIDNEY FUNCTION

Cystatin C is a 122 amino-acid protein. It has several properties that make it a good candidate for estimating glomerular filtration rate (**GFR**). Levels approximate direct measurement of GFR (as by iothalamate) more precisely than creatinine-based estimates.

It is produced steadily by all types of nucleated cells in the body. Its low molecular weight allows it to be freely filtered by the glomerular membrane. It is not secreted by the tubules, nor is it reabsorbed by the tubules.

Levels are independent of weight and height, muscle mass, age, and sex (in contrast to creatinine clearance). Measurements can be made from a single random blood sample.

Cystatin C is becoming increasingly available. Elevated serum levels (above 1 mg/L) have been considered a marker for "pre-clinical" kidney disease, especially in the community-dwelling elderly. High levels have been associated with an increased risk of cardiovascular disease and death.

This was my introduction to cystatin C. Although not a practical point at this time, I believe the potential is great.

I believe kidney function should be measured more often in elderly patients. Many will have some reduction in function. This has an important clinical application, especially in prescribing the dose of drugs which are excreted by the kidneys. I believe many elders receive too-high doses, even though the dose prescribed is the "recommended" dose. For continuing medications, a primary care treatment plan which up-titrates dosage gradually to the desired benefit is a reasonable approach.

Meanwhile, I believe that albuminuria (overt and micro-) should be measured more frequently. This is a valid marker of reduced kidney function.

DELAYED PRESCRIPTION

Another Application of the Delayed Prescription

8-5 MANAGEMENT STRATEGIES FOR ACUTE CONJUNCTIVITIS IN GENERAL PRACTICE:

A pragmatic, open, randomized, controlled trial in 30 general practices compared: 1) immediate antibiotic (chloramphenicol eye drops), 2) delayed antibiotic, or 3) no antibiotic (controls), in over 300 patients with acute infective conjunctivitis.

Use of antibiotic:	Immediate	Delayed	No antibiotic
Actually filled prescriptions	99%	53%	30%
No. (%) who believed antibiotics are very effective	67	55	47

(*Note : Only about half returned to receive a delayed prescription.*)

Delaying antibiotics for conjunctivitis in primary care was associated with similar severity and duration of symptoms and with reduced antibiotic use.

There was no difference between groups in cure rate at day 8. Outcomes in the delayed group and the control group were not significantly different.

The average score of severity of symptoms days 1-3 did not differ significantly between groups. The immediate group was more likely to believe that antibiotics were effective, and were more

likely to state they would re-attend for future conjunctivitis. (Ie. were “medicalized”.)

Significant bacterial growth was evident in 50% of swabs taken (69 of 138). No significant difference in outcomes between those positive and negative.

Conclusion; A delayed prescription is likely the most appropriate strategy in primary care.

The effect of the patient’s perception that the antibiotic “cured” the infection leads them to return for the same prescription should the infection recur, or if another infection occurs. (“Medicalization”)

Before giving a delayed prescription, U.S. primary care clinicians would likely individualize and consider the severity of the disease, and the patient’s perceived anxiety and preference. I would give the patient the option to fill the prescription immediately despite my advice that delay may be more appropriate.

I believe most U.S. primary care clinicians, when prescribing a delayed prescription, would give the patient a prescription at the first visit with the admonition not to get it filled unless the condition worsened or was not considerably improved in 2 to 3 days. This would eliminate a return visit.

The investigators, however, stated that requiring a patient to return to the office to receive the delayed prescription may have reduced antibiotic use compared with providing the prescription immediately and advising delay.

Similar investigations have reported that upper respiratory infections, acute bronchitis, and select patients with sore throat fall into the same classification—no benefit from antibiotics, and increasing “medicalization” (patients’ belief that the antibiotic actually cured), leading to additional requests for antibiotics should another infection occur.

I believe that patients are not much concerned that overuse of antibiotics will lead to development of bacterial resistance. They would likely be more concerned about adverse reactions to the drug. They should be informed about this possibility.

DEMENTIA

Should These Drugs Be Removed From General Use?

9-7 ROLE OF CHOLINESTERASE INHIBITORS IN DEMENTIA: *Needs Rethinking*

Meta-analyses show quite consistently that these drugs have modest beneficial effects compared with placebo—at six months, a mean difference of 2 to 3 points on the Alzheimer’s disease assessment scale (range 0 to 70); of 2.4 points on the assessment of activities of daily living on the progressive deterioration scale (range 0 to 100); and a difference of 2.5 points on the neuropsychiatric inventory scale (range 12 to 120). Caregivers often reported improvements in behavioral disturbances and activities of daily living in patients taking the drugs. But also when their relative-patient was taking a placebo.

Within one year, 9% of Alzheimer’s patients who were taking the drugs were admitted to care homes vs 14% of those on placebo. At three years, the numbers were almost identical—42% vs 44%.

The UK National Institute for Health and Clinical Excellence (NICE) is now considering revising the guidelines because the drugs do not provide value for money. Their benefits are, by any criteria, modest**.**

This has been met with a hostile reception from some segments of the public.

A frequent argument is that the new recommendations are wrong because the medicines are all that the doctors have to offer. “The tragedy is that the only currently licensed medicines for a cruel illness have turned out to be of marginal benefit.”

This is more a social, economic issue than medical. The modest and transient benefits of these drugs are well known. On average, they retard progression of dementia by about 6 months. They do not prevent dementia. As the article suggests, over several years, the drugs make little difference in admission to care institutions.

But, the reported outcomes in randomized trials are mean outcomes. Some patients may respond more favorably. They may be outliers. Families may hope for this. I believe, however, that many patients take these drugs for years too long.

DIABETES

“It Is Now Easier To Achieve The Recommended Hba1c Goal Of Under 7%”.

7-7 STARTING INSULIN THERAPY: *A Rational Approach*

This article reviews the pharmacological characteristics of currently available insulin products and suggests initial insulin regimens, especially for type 2 diabetes (**DM-2).** Patients with type 1 diabetes are generally more homogenous in terms of underlying pathophysiologic characteristics than those with DM-2.

The review begins by describing the pharmacologic characteristics of some of the most commonly used insulin products.

It describes 3 common blood glucose profiles of patients with DM-2 that represent typical patterns. The authors suggest an initial insulin regimen for each profile that would then be modified according to individual responsiveness. The need for an individualized approach to insulin therapy cannot be overemphasized.

All patients with type 1 diabetes require insulin. Indications for DM-2 include: symptomatic hyperglycemia, failure of oral therapy, pregnancy, acute illness necessitating surgery, cardiovascular surgery, acute myocardial infarction, and admission to intensive care.

I believe insulin should be more frequently used in patients with DM-2 to help achieve recommended HbA1c levels.

This is a helpful guide for primary care clinicians. I will file it for reference. Read the full abstract.

“To Be Taken By All Patients With Diabetes”

7-8 “POLYPILL” FOR PATIENTS WITH DIABETES

“A daily cocktail of inexpensive drugs for individuals with diabetes could save 1.2 million lives, prevent 4.5 million myocardial infarctions, reduce cases of renal failure by 600 000, and result in 1 million fewer cases of blindness or eye surgeries over the next 30 years.” (Robert A Rizza, president of the American Diabetes Assn. at the June 2006 meeting.) There is a need to overcome “physician inertia” and encourage all clinicians to treat patients with diabetes aggressively.

The “Polypill”, to be taken daily, contains metformin 1000 mg; aspirin 75 mg; a generic statin drug (eg, simvastatin 40 mg); and a generic angiotensin-converting enzyme inhibitor (eg captopril).

The "Polypill" concept remains alive. It was first proposed by Wald and Law (BMJ 2003; 326: 1419-23 Practical Pointers June 2003)—"A Strategy To Reduce Cardiovascular Risk By More Than 80%". Their Polypill contains 6 drugs to be taken daily: simvastatin 40 mg; hydrochlorothiazide 12.5 mg; atenolol 25 mg; enalapril 5 mg; folic acid 800 micrograms; and aspirin 75 mg. Patients with established cardiovascular disease, diabetes, and smokers are not the only individuals who might benefit. They also proposed that the pill would be beneficial if taken by all persons over age 55.

The diabetes polypill contains 3 of the cardiovascular polypill components (statin, aspirin, and ACE-inhibitor in addition to metformin).

7-9 NEW INJECTABLE DRUGS FOR DIABETES: Incretin mimetics—Exenatide and Pramlintide

Incretins are natural insulinotropic substances originating in the g.i. tract that are released by meals.

A. Glucagon-like peptide-1 (GLP-1): Naturally released after a meal. It promotes insulin production, reduces production of glucose, and promotes a feeling of fullness. (The natural half life = less the a minute)

B. Amylin: A natural hormone that, along with insulin, is produced by the beta cells. It helps slow the flow of sugar from the stomach into the blood and contributes to post prandial glucose control

This abstract from the 2006 PDR outlines actions of two new incretin mimetics which have recently been approved by the FDA.

1) Exenitide (*Byetta*) is a 39 amino acid peptide in which several amino acids of the natural human GLP-1 are replaced by others. It is given twice daily in microgram amounts, reaching peak levels in 2 hours. Blood levels are detectable up to 10 hours. It activates the GLP-1 receptor and, especially when added to metformin or a sulfonylurea, improves glucose control.

2) Pramlintide (*Symilin*) is a synthetic analogue of, and adjunct to, human amylin. Injected s.c. separately with insulin before meals. Approved by FDA in 2005. It is for use in patients who require insulin. It is reported to lower HbA1c slightly and to weight reduction.

Testing HbA1c More Often Than Every Several Months May be Misleading

9-5 GLYCATED HAEMOGLOBIN (HbA1c) MONITORING

This article discusses some of the physiology of HbA1c and some common situations in which it may be misleading. With increasing emphasis on achieving lower HbA1c values, clinicians need to understand its limitations.

Glycation of hemoglobin is non-linear over time. Formation of HbA1c occurs over the lifespan to the red cells (~ 120 days). Approximately 50% is present in older cells (aged 90-120 days—the end of lifespan). The other 50% occurs in younger cells (aged 1 -90 days). Thus, HbA1c represents a weighted average of blood glucose over the previous 3 to 4 months. A greater percentage is present in older cells.

The reviewers discuss several situations illustrating how HbA1c may mislead.

Testing HbA1c more often than every several months may potentially cause clinical errors.

HbA1c should *not* be used to diagnose diabetes. Indiscriminate use of HbA1c risks incorrect classification.

Two measurements a year are sufficient in patients who are meeting goals of treatment and who have stable control, and a maximum of 4 to 6 a year in patients whose treatment has changed, or who are not meeting treatment goals.

"As situations of increased hemoglobin turnover are often not stable, if the values of HbA1c are interpreted at all, they should logically be combined with home glucose measurement as an indictor of day to day control."

Read the full abstract.

Is This A Reasonable Application For Primary Care Practice?

9-10 EFFECTS OF ROSIGLITAZONE ON THE FREQUENCY OF DIABETES IN PATIENT WITH IMPAIRED GLUCOSE TOLERANCE OR IMPAIRED FASTING GLUCOSE

This 3-year study assessed whether rosiglitazone (*Avandia* 8 mg daily) would reduce the frequency of development of type 2 diabetes (**DM2**) in patients with impaired fasting glucose, impaired glucose tolerance, or both (pre-diabetes).

Both placebo and rosiglitazone groups received advice about diet and lifestyle.

	Composite outcome*	Became normoglycemic**
Rosiglitazone	11.6%	38.6%
Placebo	26%	20.5%***

* The composite outcome (development of DM2 or death) contained mainly subjects who developed diabetes. Deaths were infrequent; slightly over 1% in both groups.

** Regression of fasting plasma glucose to less than 100 mg/dL

*** Note that about 1/5 of subjects taking placebo became normoglycemic.

Absolute difference = 15.4% (NNT for 3 years to prevent one composite outcome) = 6;

NNT to achieve normoglycemia in one subject = 5)

Conclusion: Rosiglitazone reduced incident DM2 and increased the likelihood of regression to normoglycemia in adults with impaired fasting glucose or impaired glucose tolerance, or both (pre-diabetes).

This is another example of American's preference to take a "pill for their ill" rather than adopting healthy lifestyles. Pill-taking is so much easier!

Note that at baseline many subjects were obese, sedentary, had hypertension, and smoked. These risks must have been reduced in some subjects during the trial. We are not told how many, or how they were treated. These factors carry more risk than risks of pre-diabetes, and certainly should take precedence over any drug therapy to reduce risk of progression of pre-diabetes into diabetes.

What is the benefit / harm-cost ratio of rosiglitazone?

1) Benefit: The outcome of the trial does not provide any estimate of clinical benefit (reduction

in complications of diabetes or increased years of health). The endpoint of this trial was a substitute (intermediate) endpoint—a chemical outcome (difference in plasma glucose), not a clinical outcome.

2) Harm: Will come to some. The drug does cause fluid retention and has a risk of congestive heart failure.

3) Cost: By my calculation, based on price quoted by drugstore.com = $6,263.00 for 3 years. Generic Metformin 1000 mg costs $177.00 for 3 years.

The trial implies that reducing the risk of developing diabetes will produce clinical benefits. We do not know by how much. We do not know if continuing rosiglitazone beyond 3 years will reduce progression to DM2. I doubt that many patients would continue rosiglitazone after 3 years. Note that ¼ of subjects in the trial discontinued the drug during the 3 years. In clinical practice, more will discontinue. This limits applicability. I believe the risk of DM2 will revert to baseline risk when the drug is discontinued.

I would wager that, in clinical practice, patients who rely on a pill to reduce risk of DM2 would be less likely to maintain lifestyle changes to reduce risk. Lifestyle changes would be more permanent. Lifestyle interventions are essential.

How effectively would reduction in risk of developing DM2 during 3 years reduce risk of cardiovascular complication of DM2? Very little. The number needed to treat pre-diabetes over 3 years with rosiglitazone to prevent one clinical event would be extremely high.

I would not prescribe rosiglitazone for this purpose. I might prescribe metformin to very select patients as a bridge to reduce risk while they improve lifestyles over a year or two. Metformin has some advantages: no hypoglycemia; no weight gain; reduction in triglycerides; reduction in macro-vascular events. And cost.

Benefits Were Sustained for At Least 3 Years After Active Counseling Was Stopped

11-3 SUSTAINED REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES BY LIFESTYLE INTERVENTION: The Finnish Diabetes Prevention Study.

Lifestyle interventions can prevent deterioration of impaired glucose tolerance to manifest type 2 diabetes (**DM2**), at least as long as the intervention continues.

This study assessed whether the originally-achieved risk reductions from lifestyle interventions remain after discontinuation of active counseling.

The first phase of the study entered 522 overweight men and women (mean age = 55; BMI = 31) between 1993 and 1998. All had impaired glucose tolerance, based on a 75 gram oral glucose tolerance test. (2-hour plasma glucose between 140 and 199 mg/dL; 7.8 and 11.0 mmol/L)

The intervention cohort received individualized, detailed counseling about diet and exercise. Counseling continued intermittently for the 4 years. Controls were given general health behavior information without specific, individualized advice.

The first phase of the study lasted a median of 4 years at which time the incidence of DM2 was lower in the intervention group. This second phase of the study reports outcomes of the 2 groups for the additional 3 years (years 4 to 7) during which subjects received no counseling.

During years 4 to 7, incidence rates per 100 person-years = 4.3 in the former intervention group, and 7.4 in the former control group

A modest difference in body weight between intervention and control groups was maintained during the final 3 years (- 1.8 kg vs 0 kg loss). The benefits of the intervention were largely, but not entirely, mediated through weight loss.

This is an important message from the public health point of view. Interventions can have long-term effects on lifestyle.

Conclusion: Lifestyle intervention in people at high risk for DM2 resulted in sustained lifestyle changes and a reduction in incidence of DM2, which remained after individual lifestyle counseling was stopped.

I spent considerable time studying and abstracting this study. I believe the message is important. Patients can achieve and maintain favorable lifestyles which will reduce risk of DM2 and (more importantly) reduce average glucose levels. I doubt, however, that most primary care clinicians have the time to devote to an intensive effort. But they can constantly remind their high-risk patients about their risky lifestyles. And help to arrange continuing counseling by other health-care workers.

No Reason To Be Concerned About Diuretic-Associated Increase In Risk Of Diabetes.

11-5 FASTING GLUCOSE LEVELS AND INCIDENT DIABETES MELLITUS IN OLDER NON-DIABETIC ADULTS RANDOMIZED TO RECEIVE 3 DIFFERENT CLASSES OF ANTI-HYPERTENSIVE TREATMENT

Elevated blood glucose levels have been associated with thiazide-type diuretics.

This post-hoc subgroup study compared the effects of *first-step* therapy with a thiazide (chlorthalidone), an angiotensin converting enzyme-inhibitor **(ACE-I;** lisinopril), and a calcium channel blocker (**CCB;** amlodipine**)** on fasting glucose and incident type 2 diabetes (**DM2**) in elderly patients with hypertension. And determined associated cardiovascular and renal disease risks.

The differences in mean fasting glucose (**FG)** were small: +3 mg/dL between chlorthalidone and amlodipine and + 5 mg/dL between chlorthalidone and lisinopril.

There was no effect of these changes in FG on cardiovascular (**CVD**) and renal outcomes." This suggests that diuretics lead to elevated glucose levels by mechanisms different from those associated with DM."

Development of DM2 (% with FG above 125 mg/dL): chlorthalidone 14; amlodipine 12; lisinopril 11.

Hazard ratios associated with subjects who developed DM2 vs those who did not develop DM2 during the first 2 years with subsequent cardiovascular disease:

	Chlorthalidone	Amlodipine	Lisinopril
CHD	1.46	1.71	2,23
Stroke	1.83	2.63	0.48
Heart failure	0.96	1.29	3.66
Combined cardiovascular disease	0.96	1.14	1.31
Total mortality	1.05	1.92	1.31

Although none were statistically significant, this suggests that outcomes in patients taking chlorthalidone may be more favorable than in patients taking the other drugs.

Conclusion: FG levels increase in older adults with hypertension regardless of the treatment type. Compared with the other drugs, chlorthalidone modestly increased the risk of FG above 125 mg/dL (DM) There was no conclusive or consistent evidence that this chlorthalidone-associated increase in DM increased risk of clinical events over 5 years.

I believe this is an important clinical point, well worth the time I spent studying and abstracting the article. I believe that judicious use of thiazides remain the cornerstone of treatment for hypertension. Start low and go slow (eg, up to 25 mg hydrochlorothiazide). I would add a second and third drug rather than increasing the dose of the thiazide.

There must have been two different types of DM in the chlorthalidone group: 1) That as a result of the drug, and 2) That which, as age of the cohort increased, occurred spontaneously – not related to the diuretic. The study concerned only group 1).

"Thiazides Become The Cornerstone"

11-6 NEW-ONSET DIABETES MELLITUS LESS DEADLY THAN ELEVATED BLOOD PRESSURE?

The evidence that thiazide therapy is effective for treatment of hypertension passes numerous standards, including pharmacological and mechanistic plausibility, robust outcomes in heterogeneous groups of patients, favorable results in head-to-head comparison with other agents, and efficacy in combination therapy trials.

In all stages of hypertension and in the elderly population, thiazide-based therapy significantly reduces risk of stroke, coronary events, congestive heart failure, renal failure, and malignant hypertension.

While the occurrence of new-onset DM is an independent predictor of cardiovascular risk, administration of diuretics is not independently associated with cardiovascular risk. The recent guidelines from the British Hypertension Society state: "It is not clear that an elevated blood glucose developing as a consequence of drug treatment has the same long-term health impact as in other circumstances."

"Indeed, evidence is mounting that diuretic-induced DM may be completely benign".

"This finding bolsters the concept that thiazide-induced DM is a different and benign disease entity compared with either do novo DM, or that which develops in the context of other antihypertensive agents."

ALLHAT found that thiazide was more effective in lowering BP than either CCB or ACE. We might conclude that the benefit of BP reduction outweighs any risk associated with development of DM.

"Viewed through the wide-angle lens of outcomes research, thiazides become the cornerstone on which blood pressure-lowering treatment should be built."

I believe the benefit / harm –cost ratio of judicious use of thiazides as a first-line drug for hypertension is higher than other antihypertension drugs.

"Lifestyle Counseling And Metformin Should Be Started At The Same Time"

12-4 MANAGEMENT OF HYPERGLYCAEMIA IN TYPE 2 DIABETES

The authors present an algorithm to achieve good glycemic control:

Lifestyle counseling and metformin

Add sulfonylurea or thiazolidinedione or basal insulin

HbAic 7% and above

Metformin	Metformin	Intensify insulin
+	+	
sulfonylurea	thiazolidinedione	
+	+	
basal insulin	sulfonylurea	
	OR	
	metformin	
	+	
	thiazolidinedione	
	+	
	basal insulin	

HbAic still 7% and above

Intensify insulin + metformin + or - thiazolidinedione

Treatment of hyperglycemia in DM2 is complex. Combinations of glucose lowering drugs are often needed to achieve and maintain blood glucose at target levels. Development of new drugs has increased treatment options, and has contributed to the uncertainty surrounding new therapeutic approaches.

The traditional approach to lowering blood glucose consists of an ordered sequence: lifestyle modifications; oral monotherapy; oral combination therapy; and finally insulin (with or without oral drugs). This strategy usually results in recurrent failure because patients are allowed to become hyperglycemic before the next step is considered. "The aim should be to keep glycemic levels as near to normal as possible."

Metformin is widely accepted as the first line drug. It is relatively effective, safe, and cheap. It may be associated with a decrease in cardiovascular disease in obese persons with DM2. It does not cause weight gain, and may be associated with weight loss.

Conclusion: The burden of DM2 can be prevented by stringent control of hyperglycemia and other cardiovascular disease risk factors. Treatment needs to focus on maintaining blood glucose values as close to the non-diabetic range as possible, with early initiation of effective drugs (combinations of oral drugs and insulin). And prompt adjustment of treatment when HbA1c is above target.

This is an eminently practical clinical review, I wish for more like it.

Newer compounds are not included because of limited evidence and high costs.

The new therapies made available over the years to treat DM2 have been amazing. I believe most primary care clinicians will stick to the old standbys. And await further experience to tell if any newer drugs provide better control and more favorable outcomes than the old standards.

We can now do much to reduce the devastating complications of diabetes with control of other cardiovascular risk factors and glycemia. This is a major challenge for primary care.

A New Drug Class for Treatment of Type 2 Diabetes.

12-5 THE INCRETIN SYSTEM: GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS AND DIPEPTIDYL PEPIDASE-4 INHIBITORS IN TYPE 2 DIABETES

This article reviews the action of glucagon-like peptide (**GLP**). GLP is a normally produced incretin—a human gut-derived hormone that:

1) Stimulates insulin production and suppresses glucagon secretion
2) Inhibits gastric emptying
3) Reduces appetite and food intake

Drugs have been developed to enhance GLP action:

1. GLP receptor agonists. (Termed incretin mimetics)
2. Inhibitors of the enzyme which degrades GLP, and prolongs GLP action. (Incretin enhancers)

I abstracted the article briefly to introduce a newly FDA-approved inhibitor of the enzyme which degrades GLP and thus increases its activity (Januvia; sitagliptin phosphate; an incretin enhancer; Merck). Januvia is being advertised. It is a once-a-day orally effective agent approved as mono-therapy for type 2 diabetes, and as an add-on to other drugs.

The recommended dose is 100 mg once a day with or without food. It works only when blood glucose in elevated, It enhances insulin production by the pancreas, and reduces uncontrolled production of glucagon and thus decreases glucose output from the liver.

Adverse effects are similar to placebo. The most common are stuffy or runny nose, sore throat, upper respiratory infection, and headache.

Used as an add-on to metformin, Januvia led to a greater reduction in HbA1c than metformin alone. It also reduced post meal glucose levels and fasting blood glucose.

Treatment was not associated with weight gain or increased risk of hypoglycemia.

This information comes from a press release by Merck. I would not prescribe Januvia at this time. I believe it adds little benefit above that of well established antidiabetes drugs. Several more years of use by the general public are required to establish effectiveness and safety

"May Increase The Potential For Improving Glycemic Control In The Diabetes Population"

12-6 EFFICACY AND SAFETY OF INHALED INSULIN THERAPY IN ADULTS WITH DIABETES MELLITUS: *A Meta-Analysis*

The FDA approved inhaled insulin one year ago for use in non-smokers, and in patients without pulmonary disease. Because of its pharmacokinetic profile it has been studied as a pre-meal alternative to injections of regular or rapid-acting insulin.

Comparisons:

Inhaled insulin vs subcutaneous insulin:

Small difference in decrease in HbA1c favored subcutaneous insulin. (Mean difference = 0. 08%)

No difference in proportion of patients achieving the goal of HbA1c under 7%. (25% vs 27%)

Inhaled insulin vs oral agents:

Three studies showed a large difference in HbA1c favoring inhaled insulin (mean difference = 1.45%)

Two studies showed only a small difference (0.20%) favoring inhaled insulin. These trials included more subjects, and were of longer duration.

Subjects with DM2 taking inhaled insulin were more likely to achieve HbA1c under 7%. (31% vs 17%).

Safety:

A. Severe hypoglycemia:

Inhaled insulin vs subcutaneous insulin:

Patients with DM1 patients in both groups experienced more episodes of severe hypoglycemia than patients with DM2. Little difference between inhaled and injected

	Inhaled	Injected
DM1	75%	78%
DM2	16%	18%

Severe hypoglycemia was more commonly reported in patients using inhaled insulin vs oral agents:

Inhaled 9% Oral 4%

B. Pulmonary safety:

The most common pulmonary symptom was a nonproductive cough (17%). Cough occurred within seconds to minutes. It was mild and not associated with changes in pulmonary function. Cough diminished over time.

FEV1 decreased from baseline (mean reduction = 0.03 L). FEV1 decreased slowly over 6 months, but was stable thereafter.

A few discontinued inhaled insulin because of respiratory events.

Conclusion: Inhaled insulin had slightly less efficacy in glycemic control than subcutaneous regular insulin.

Patient-acceptance was increased. “Until long-term safety data are available, inhaled insulin should be reserved for nonpregnant adults with diabetes who are opposed to injections and who would otherwise delay appropriate and timely therapy with insulin.”

All trials comparing inhaled insulin vs subcutaneous insulin included injected long-acting insulin in addition to inhaled insulin in the inhaled insulin group.

And the majority of trials comparing inhaled insulin vs oral agents included continuation of oral agents in the treatment group.

Administration of inhaled insulin is not simple. There must be a learning curve. It may take some weeks before dose is titrated to obtain maximum efficacy and safety.

COST: At my pharmacy a starter kit containing an inhaler, a replacement chamber, 180 1-mg blisters (equivalent to 3 U regular insulin) , and 90 3-mg blisters (equivalent to 8 U regular insulin) costs $188.00

Please read the full abstract !

DIASTOLIC HEART FAILURE (See HEART FAILURE)

DIET

"A Higher Glycemic Load Was Strongly Associated With An Increased Risk Of CHD"

11-4 LOW-CARBOHYDRATE-DIET SCORE AND THE RISK OF CORONARY HEART DISEASE IN WOMEN

This study evaluated data in the Nurses Health Study (> 82 000 women) which permitted comparison of a low carb, higher fat, higher protein diet with a high carb, lower fat, lower protein diet.

All subjects had completed validated food-frequency questionnaires several times during the study.

Divided mean daily intakes of carbohydrate, protein and fat into deciles beginning with the lowest intake of carbs, and progressing to the highest. (*1990 questionnaire data*):

Decile with lowest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1539	37%	40%	23%

Glycemic load

73

Decile with highest carb intake

Total kcal	Energy from carb	Energy from fat	Energy from protein
1814	59%	26%	15%

Glycemic load

145

Also determined the % of energy of animal fat and vegetable fat, and animal protein and vegetable protein for

each decile of carb intake:

Over 20 years (over 1 500 000 person-years), documented 1994 new cases of CHD.

On average, body mass index increased from baseline over 20 years by about 2.5 units *regardless* of the carbohydrate intake.

After controlling for multiple potential confounders, the relative risk (RR) of coronary heart disease between

those in the highest intakes of carbohydrate (lowest fat) vs those in the lowest intake of carbohydrate (highest fat) was 0.94. (No statistically significant difference.) "Total dietary fat has not been associated with a risk of coronary heart disease." *(Ie, in this study, no evidence that diets low in carb and higher in fat and protein were associated with increased risk of CHD.)*

A higher glycemic load was strongly associated with an increased risk of CHD. (RR of highest glycemic load
vs lowest = 1.90 vs 1.00, (*Almost double*)

"We found that, after taking into account confounding variables, a low carbohydrate diet (*higher fat*) was *not*
associated with a risk of coronary heart disease in this large prospective cohort of women."

When vegetable sources of fat were chosen, a low carbohydrate intake was associated with a moderately *lower* risk of CHD than when animal sources of fat were chosen. (RR = 0.70)

Conclusion: Diets lower in carbohydrate and higher in protein and fat were *not* associated with increased risk of CHD in women. When vegetable source of fat and protein were chosen, the RR of CHD was lower than when animal fat and animal protein were chosen. Low glycemic load diets were associated with a lower risk of CHD.

This remarkable study is more complicated than I have indicated. It was difficult to abstract. I believe I have captured the essence of the outcomes.

The study points out that a low glycemic load diet is part of a healthy diet. Higher levels of plasma glucose are a risk factor.

It confirms that a low saturated fat diet is healthier, and that vegetable fats (oils; mono-unsaturated fat) and polyunsaturated fats are also important parts of the healthy diet.

It also confirms how difficult it is to lose weight on any diet, and to maintain the loss.

The healthy diet:

1) Low glycemic load

2) Low saturated fat; high poly- unsaturated fat, and mono-unsaturated fat

3) Zero trans fat

4) Total calories adjusted to maintain BMI under 25

Add a glass of wine before dinner, and this is similar to the Mediterranean diet.

DIASTOLIC HEART FAILURE (See HEART FAILURE)
DIPEPTIDYL-PEPTIDASE-INHIBITORS (See DIABETES)

DRUG THERAPY

7-12 A META-ANALYSIS OF THE ASSOCIATION BETWEEN ADHERENCE TO DRUG THERAPY AND MORTALITY

Poor adherence to therapy is considered a critical barrier to treatment success. Good adherence to a beneficial drug must be associated with good health outcomes. Individual studies have reported that good adherence (even to placebo) is associated with a reduction in risks. “This is contrary to the proposition that placebo has little effect on health outcomes, and has led to the speculation that adherence to drug therapy may act as an identifiable marker for overall healthy behavior, the so called ‘healthy adherer’ effect.”

This study evaluated the relation between adherence to drug therapy, including placebo, and mortality.

A. Deaths overall to drug therapy:

Good adherers 1462 of 31 439 (4.7%)

Poor adherers 1317 of 15 408 (8.5%)

(Good adherence [vs poor adherence] to a beneficial drug therapy resulted in 3.8% reduction in death.

Of 1000 patients with good adherence, 38 (one in 26) would have their lives extended merely because of some attribute good adherers possess.)

B. Deaths in the placebo groups--eight studies with a placebo arm (19 633 participants):

Good adherers to placebo 4.3% (584 of 13 429)

Poor adherers to placebo 6.5% (415 of 6204)

(Ie, good adherence to placebo was associated with a reduction in mortality of 2.2%

Of 1000 subjects, some attribute of good adherers prolonged life in 22 (one in 45).

C. Conversely, Good adherence to a therapy which eventually was proven to be *harmful* resulted in an *increased* mortality.

Good adherence may be a marker of overall healthy behavior.

By definition, placebos have no pharmacological effects. They may have profound psychological effects. If one believes in a treatment (which is really a placebo), will outcomes be better than if one does not believe? It depends, I suspect, on the nature of the disease and the power of the practitioner. (Consider the power of the Shaman.) I believe also that patients adhere better if they and the clinician have a good relationship. They also tend to report good effects when they wish to please the practitioner.

Take 1000 patients receiving placebo: 1) 500 adhere conscientiously; 2) 500 do not adhere regularly. Outcomes will be better in 1).

EJECTION FRACTION (See HEART FAILURE)

ENERGY EXPENDITURE

The Higher the FLAEE, the Lower the Risk Of Death.

7-14 DAILY ACTIVITY ENERGY EXPENDITURE AND MORTALITY AMONG OLDER ADULTS

The most accurate method of determining free-living energy expenditure uses isotopes of ^{2}H and ^{18}O

($^{2}H2^{18}O$—doubly labeled water). ^{2}H is eliminated as water, and ^{18}O is eliminated as water and carbon dioxide. The excess disappearance rate of ^{18}O relative to ^{2}H is a measure of the carbon dioxide production rate, a direct measure of total energy expenditure.

To calculate the "free living activity energy expenditure" (**FLAEE**—the amount an individual expends in any activity per day), the investigators determined resting metabolic rate and calculated the thermic effect of meals, and subtracted these energy expenditures from the total. This objectively determined the FLAEE.

FLAEE captures *any form* of physical activity ranging from purposeful exercise to simple fidgeting. Physical activity questionnaires generally address only the former.

Over a 2-week period, this study determined the FLAEE of over 300 adults (mean age 75) twice over a 2-week period in 1997-98. All were healthy enough to climb stairs and walk, and to perform activities of daily living independently. None had mobility disabilities.

Divided the subjects into 3 categories, depending on their FLAEE:

High	> 770 kcal/day
Middle	521 – 770 kcal / day
Low	< 521 kcal / day.

Followed subjects for all-cause mortality over a mean of 6 years.

Absolute risk of death was 12% in the highest tertile of FLAEE; 18% in the middle tertile; and 25% in the lowest tertile. For every 287 kcal / day of FLAEE, there was about a 30% lower risk of mortality. This would be attained by performing about 1 ¼ hours of activity per day at a metabolic rate of 3.0—household chores, vacuuming, mopping, washing windows, lawn work, walking at 2.5 MPH, and non-sitting work. In this study, the total self reported activity duration was about 30 to 60 minutes longer on average in the 2nd and 3rd tertiles than in the 1st.

This study, which suggests that *any activity* expenditure in older adults can lower mortality rates, seemingly contradicts reports that exercise needs to be performed at a specific intensity.

"More important, this accumulation is from usual daily activities that expend energy and not necessarily for volitional exercise." Simply expending energy through any activity may influence survival.

OK, all you senior citizens, keep moving !

ESTROGEN (See HORMONE REPLACEMENT THERAPY)

EVIDENCE-BASED MEDICINE

"Most Proponents Of E-BM Adopt A Balanced View."

11-11 ANALOGIES BETWEEN READING OF MEDICAL AND RELIGIOUS TEXTS

Conventional medicine can be seen as a belief system characterized by a profession of faith in evidence-based medicine (**E-BM**). Faith in E-BM follows from the benefits it has delivered in the past, and continues to deliver. It is the best method we have for navigating our way through potential new treatments.

E-BM is analogous to many religious traditions. It is a canon of sacred texts (medical literature). Differences in interpretation can often be traced to different assumptions underlying our reading of the literature.

Just as there are fundamentalist, conservative, and liberal views of religious texts, there are fundamentalist, conservative, and liberal views of E-BM.

The editorialist goes on to describe some analogies between religious fundamentalism and medical fundamentalism.

Most proponents of E-BM adopt a balanced view. They emphasize the limitations of E-BM, the need for judgment in applying it to individual patients, and the validity of evidence other than randomized, controlled trials. They tend to see the literature as a guide, establishing principles that need to be applied to specific situations.

Randomized, controlled trials may show a consistent improved survival for a defined period. "The main difficulty in applying these data is the external validity." How should we treat the patients with serious co-morbidity? And patients who do not meet inclusion criteria of the trial?

I enjoyed abstracting this commentary. I felt, however, that the editorialist painted the analogy with too broad strokes. Medical fundamentalism is not that "fundamental". I do not believe that primary care clinicians are strict "medical fundamentalists". Most will be selective in applying the treatment provided to subjects in a randomized-controlled trial (RCT). They know that their individual patient may vary from patients entered into the trial. Their individual patient may well be an outlier.

Some individuals will gain a more favorable response than the mean response to the intervention. Some will gain less. Some may be at greater risk of developing an adverse outcome if not treated. Some will be at greater risk of harms if treated.

There are also many social and economic reasons why the treatment recommended by the RCT cannot be applied to an individual patient.

Primary care practice is difficult to do well.

Read the full abstract. Read the original article.

FERRITIN (See ANEMIA)

FITNESS

The Higher the FLAEE, the Lower the Risk Of Death.

7-14 DAILY ACTIVITY ENERGY EXPENDITURE AND MORTALITY AMONG OLDER ADULTS

The most accurate method of determining free-living energy expenditure uses isotopes of ^{2}H and ^{18}O ($^{2}H2^{18}O$—doubly labeled water). ^{2}H is eliminated as water, and ^{18}O is eliminated as water and carbon dioxide. The excess disappearance rate of ^{18}O relative to ^{2}H is a measure of the carbon dioxide production rate, a direct measure of total energy expenditure.

To calculate the "free living activity energy expenditure" (**FLAEE**—the amount an individual expends in any activity per day), the investigators determined resting metabolic rate and calculated the thermic effect of meals, and subtracted these energy expenditures from the total. This objectively determined the FLAEE.

FLAEE captures *any form* of physical activity ranging from purposeful exercise to simple fidgeting. Physical activity questionnaires generally address only the former.

Over a 2-week period, this study determined the FLAEE of over 300 adults (mean age 75) twice over a 2-week period in 1997-98. All were healthy enough to climb stairs and walk, and to perform activities of daily living independently. None had mobility disabilities.

Divided the subjects into 3 categories, depending on their FLAEE:

High	> 770 kcal/day
Middle	521 – 770 kcal / day
Low	< 521 kcal / day.

Followed subjects for all-cause mortality over a mean of 6 years.

Absolute risk of death was 12% in the highest tertile of FLAEE; 18% in the middle tertile; and 25% in the lowest tertile. For every 287 kcal / day of FLAEE, there was about a 30% lower risk of mortality. This would be attained by performing about 1 ¼ hours of activity per day at a metabolic rate of 3.0—household chores, vacuuming, mopping, washing windows, lawn work, walking at 2.5 MPH, and non-sitting work. In this study, the total self reported activity duration was about 30 to 60 minutes longer on average in the 2nd and 3rd tertiles than in the 1st.

This study, which suggests that *any activity* expenditure in older adults can lower mortality rates, seemingly contradicts reports that exercise needs to be performed at a specific intensity.

"More important, this accumulation is from usual daily activities that expend energy and not necessarily for volitional exercise." Simply expending energy through any activity may influence survival.

OK, all you senior citizens, keep moving !

GLOMERULAR FILTRATION RATE

An Emerging, Simple Marker of Kidney Function. Better than Creatinine-based Estimates

8-12 CYSTATIN C, GLOMERULAR FILTRATION RATE, and DECREASED KIDNEY FUNCTION

Cystatin C is a 122 amino-acid protein. It has several properties that make it a good candidate for estimating glomerular filtration rate (**GFR**). Levels approximate direct measurement of GFR (as by iothalamate) more precisely than creatinine-based estimates.

It is produced steadily by all types of nucleated cells in the body. Its low molecular weight allows it to be freely filtered by the glomerular membrane. It is not secreted by the tubules, nor is it reabsorbed by the tubules.

Levels are independent of weight and height, muscle mass, age, and sex (in contrast to creatinine clearance). Measurements can be made from a single random blood sample.

Cystatin C is becoming increasingly available. Elevated serum levels (above 1 mg/L) have been considered a marker for "pre-clinical" kidney disease, especially in the community-dwelling elderly. High levels have been associated with an increased risk of cardiovascular disease and death.

This was my introduction to cystatin C. Although not a practical point at this time, I believe the potential is great.

I believe kidney function should be measured more often in elderly patients. Many will have some reduction in function. This has an important clinical application, especially in prescribing the dose of drugs which are excreted by the kidneys. I believe many elders receive too-high doses, even though the dose prescribed is the "recommended" dose. For continuing medications, a primary care treatment plan which up-titrates dosage gradually to the desired benefit is a reasonable approach.

Meanwhile, I believe that albuminuria (overt and micro-) should be measured more frequently. This is a valid marker of reduced kidney function.

GLUCAGON-LIKE-PEPTIDE RECEPTOR AGONIST (See DIABETES)
GLYCATED HEMOGLOBIN (See DIABETES)

HbA1C (See DIABETES)

HEART FAILURE

"May Become the Most Common Form of Heart Failure."

7-10 OUTCOME OF HEART FAILURE WITH PRESERVED EJECTION FRACTION.

HF with preserved ejection fraction **(HFwPEF)** is increasingly recognized. It has been attributed to abnormalities of diastolic function, although the exact mechanism is debated. The term "heart failure with preserved ejection fraction" has replaced the older term "diastolic heart failure".

This study enrolled over 2800 patients (mean age 73) admitted to hospitals from 1999 to 2001. All had a discharge diagnosis of heart failure as defined by the Framingham Study criteria. Ejection fractions **(EF)** had been measured in all patients

Categorized patients into 3 groups:

1) EF less than 40% [HF with reduced EF—classical HF. Mean EF = 26%]
2) EF 40% to 50% [HF with borderline EF]
3) EF over 50% [HF with preserved EF—"diastolic" HF. Mean EF = 62%]

Clinical characteristics:

Presenting symptoms were largely similar between the groups

Patients with HFwPEF were more likely to be older (age 75 vs 72), to be female (66%), to have had hypertension (55% vs 49%) , and atrial fibrillation (32% vs 24%).

Mortality rates between group 1) and group 3) at one year were similar: 26% and 22%. Readmission rates for HF were also similar.

Thirty day mortality rates were also similar between the two groups.

A substantial proportion of patients admitted with heart failure had an ejection fraction over 50%. Their mortality rate was similar to those with reduced ejection fraction.

The association with hypertension may be due to myocardial hypertrophy which leads to limitation of ventricular filling.

The basic abnormality of congestive heart failure is a reduction in the volume of blood ejected into the general circulation from the left ventricle (stroke volume), not diastolic function. According to PeterLiu, Toronto University (personal communication) there have not been good specific studies documenting stroke volume as related to development of congestive heart failure. We have been locked into the concept of ejection fraction because it is easily determined. One can have a deficit of stroke volume from either decreased proportion being ejected, or decrease filling volume to start with.

What's in A Name? Heart Failure by Any Name Is Just as Deadly

7-11 DIASTOLIC HEART FAILURE—A Common and Lethal Condition

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

Although the AHA has revised the terminology to "heart failure with preserved ejection fraction", this editorialist still prefers the term "diastolic heart failure" (**DHF**). DHF describes the dominant underlying pathophysiological features, and has connotations familiar to clinicians. Virtually all patients with DHF will show abnormalities in diastolic function and elevated left ventricular filling pressure.

Treatments for DHF are emerging (eg, the use of angiotensin-receptor blockers). Preventive measures have proven efficacy (eg, treatment of hypertension).

Early treatment of hypertension is becoming more urgent in recognition of its role in DHF.

The basic abnormality of congestive heart failure is a reduction in the volume of blood ejected into the general circulation from the left ventricle (stroke volume), not diastolic function. According to Peter Liu, Toronto University (personal communication) there have not been good specific studies documenting stroke volume as related to development of congestive heart failure. We have been locked into the concept of ejection fraction because it is easily determined. One can have a deficit of stroke volume from either decreased proportion being ejected, or decrease filling volume to start with.

A Major Therapeutic Application—If Confirmed

11-1 STATIN THERAPY AND RISKS OF DEATH AND HOSPITALIZATION IN CHRONIC HEART FAILURE

Increasing attention has focused on potentially "pleotropic" effects of statin drugs. (Ie, effects other than on lipids.)

This study assessed whether statin therapy has beneficial effects on clinical outcomes in patients with HF.

Entered a cohort of over 24 000 patients with documented chronic HF (mean age = 70; age range 20 to > 80) to evaluate any association between *initiation* of statin therapy (after diagnosis of HF) and death and hospitalization for HF.

None had taken statins before onset of HF and entrance into the study.

Follow-up = a median of 2.4 years.

Using an intent-to –treat approach, incident statin use was associated with lower risk of death and hospitalizations (adjusted for multiple possible confounding variables).

Risks per 100 person-years	Statin use	No statin
Death	15	25
Hospitalizations for HF	22	31

(Absolute differences = ~ 10% per year; NNT to benefit one patient = 10)

Alterations of lipid levels are the major reason for prescribing statins. Other, non-lipid effects of statins may be beneficial in patients with HF (Eg, reduction in inflammatory factors and detrimental cytokines; improvement of endothelial function; stabilization of coronary plaques.)

The observed beneficial association was prominent among patients with coronary heart disease (**CHD**) as well as without known CHD.

Conclusion: Among adults who had no prior statin use, *incident* statin use after diagnosis of HF was independently associated with lower risks of death or hospitalization among patients with or without coronary heart disease.

These results are startling. I believe they call for confirmation as soon as possible. This could be a major therapeutic intervention. What should primary care clinicians do in the meantime? Since statins would be indicated for lipid control in most patients with HF, I believe we should prescribe them for almost everyone with HF.

HEPARIN (See VENOUS THROMBOSIS)

HERPES ZOSTER (See SHINGLES)

HIP FRACTURE

Associated With An Increase In Hip Fracture.

12-8 LONG-TERM PROTON PUMP INHIBITOR THERAPY AND RISK OF HIP FRACTURE

Millions of people are taking PPIs continuously, and long –term. PPI use leads to hypochlorhydria, particularly among elderly people who may have decreased PPI clearance. Hypochlorhydria could lead to calcium malabsorption, low bone mineral density, and increased risk of fracture.

This case-control study compared users of PPI and non-users, all over age 50.

Cases—patients with incident hip fracture (n = 13 556).

Controls—matched to cases (n = 135 000).

Compared PPI use in cases vs controls. Main outcome = risk of hip fracture associated with PPI use.

The adjusted odds ratio for hip fracture associated with more than 1 year of PPI use was 1.4.

The strength of the association rose with duration of PPI use:

PPI use	1 year	2 years	3 years	4 years
Odds ratio	1.2	1.4	1.5	1.6 (Adjusted for some possible confounders)

The risk of hip fracture was markedly increased among *long-term* users of *high-dose* PPI as compared with non-users of acid-suppression. (Odds ratio = 2.7)

Gastric acid may be important for absorption of insoluble calcium. Calcium malabsorption secondary to acid suppression by PPI therapy may potentially explain the association.

Conclusion: Long-term PPI therapy, particularly at high doses, was associated with an increase in hip fracture.

I believe this is a valid clinical point. Patients fitting these criteria should receive calcium and vitamin D supplementation long-term, and more liberal recommendations for use of bisphosphonates.

HUMAN IMMUNE DEFICIENCY SYNDROME (HIV)

"All Patients Should Be Screened Regardless Of Whether They Seem To Be At Risk"

9-12 CDC RECOMMENDS OPPORTUNISTIC HIV TESTING

The CDC has issued new recommendations designed to make voluntary HIV screening on an opportunistic basis a routine part of medical care for all patients aged 13 to 64. The objective is to increase early diagnosis among the estimated 250 000 Americans who are HIV positive, but are not aware of it. This would lead to earlier diagnosis and more effective treatment.

The main recommendations:

1) All patients should be screened regardless of whether they seem to be at risk.

2) Patients should be able to opt out of screening.

3) The need for special consent should be eliminated, and be replaced by a standard requirement for consent.

4) Counseling on HIV before and after the test is advisable, but not mandatory.

Making the test a normal part of care is an important step toward removing the stigma associated with testing.

Several questions arise:

Who pays?

Are satisfactory arrangements available for follow-up and treatment?

What is the gold standard for the test used?

What about false positive tests?

Does the primary care clinician have the duty to inform and to warn sexual partners of a patients tested positive?

This reminds me of the old requirements for screening for syphilis which were in place in many states years ago. In North Carolina, it was a requirement for a marriage license.

"Now, More Than Ever, HIV Care Is Primary Care."

9-13 THE CHANGING FACE OF HIV CARE

Management of HIV infections has advanced dramatically. Related morbidity and mortality has declined—attributed to improved prophylaxis against opportunistic infections, and the introduction of a potent combination of antiretroviral therapies (HAART; highly active antiretroviral therapy).

Some authorities have reported that the life expectancy of patients with HIV is approximating that of the general population. "HIV is becoming a chronic disease."

The physician of choice has changed. Earlier, infectious disease experts, oncologists, and palliative care specialists treated most patients. Now, as patients with HIV live much longer, they are developing non-HIV conditions (hypertension, cancer, diabetes, and coronary heart disease). In addition, anti-retroviral drugs are associated with dyslipidemia, diabetes, and neuropathies. As life expectancy and state of health improves, and life is extended, HIV patients may eat more and become overweight, with the same consequences.

HYPERGLYCEMIA (See DIABETES)

HYPERTENSION

. 7-4 EVOLUTION OF HYPERTENSIVE DISEASE: *A Revolution In Guidelines*

The National Institute for Health and Clinical Excellence (NICE) of the UK presents these guidelines"

Drug treatment is stratified by age.

A. Older patients:

Step 1: A calcium channel blocker or a thiazide diuretic.

Step 2: ACE* + CCB, or CCB + diuretic

Step 3: ACE + CCB + diuretic

* Angiotensin converting enzyme inhibitor. An angiotensin II blocker may be substituted.

In older patients the two most clinically effective and cost-effective drugs for initial lowering of BP are a calcium-channel blocker and a thiazide-type diuretic. BP in older patients is more resistant to therapy. The need for 2 or more drugs in most people was acknowledged.

B. Younger patients:

Step 1: ACE inhibitor

Step 2: ACE + CCB. or ACE + diuretic

Step 3: ACE + CCB + diuretic

Start with lifestyle changes.

When (at what age) to add drugs is a clinical decision based on the individual. A firm diagnosis of hypertension should be made. Monitoring with a 24-hour machine or repeated self-measurements at home are the most reliable diagnostic methods.

I believe that many patients are treated unnecessarily with drugs, and many more who require treatment do not receive them. I also believe that many patients receive too-high doses of antihypertension drugs. Lower doses can be effective, especially if a combination of drugs is used.

I would not eliminate beta-blockers from the protocol. They are beneficial and inexpensive drugs. Small doses should be used and titrated.

I believe that doses of all drugs should be carefully titrated. (Younger patients have more time to do so.)

Titration can be done in two ways:

1) Start with the usual recommended doses and titrate down according to home measurements of BP.

2) Start with low doses and gradually increase.

Staring with low doses and titrating upward would lead to fewer adverse effects and reduce costs. I would add low doses of a second and a third drug before titrating the first drug up to full doses.

A pill cutter is essential. A home monitor is essential.

The criterion for the drugs used and their doses = what works for the individual. I would add a second and a third drug at low doses rather than increase the dose of the first drug.

Since these drugs are used for a lifetime, expense is a consideration.

NICE can be accessed at www.nice.org.uk Search for clinical guideline 34 hypertension
The appendix pages 44 and 45 present a management flowchart for hypertension and the guideline for choosing drugs for newly diagnosed patients

11-5 FASTING GLUCOSE LEVELS AND INCIDENT DIABETES MELLITUS IN OLDER NON-DIABETIC ADULTS RANDOMIZED TO RECEIVE 3 DIFFERENT CLASSES OF ANTI-HYPERTENSIVE TREATMENT

Elevated blood glucose levels have been associated with thiazide-type diuretics.

This post-hoc subgroup study compared the effects of *first-step* therapy with a thiazide (chlorthalidone), an angiotensin converting enzyme-inhibitor **(ACE-I;** lisinopril), and a calcium channel blocker (**CCB;** amlodipine**)** on fasting glucose and incident type 2 diabetes (**DM2**) in elderly patients with hypertension. And determined associated cardiovascular and renal disease risks.

The differences in mean fasting glucose (**FG)** were small: +3 mg/dL between chlorthalidone and amlodipine and + 5 mg/dL between chlorthalidone and lisinopril.

There was no effect of these changes in FG on cardiovascular (**CVD**) and renal outcomes." This suggests that diuretics lead to elevated glucose levels by mechanisms different from those associated with DM."

Development of DM2 (% with FG above 125 mg/dL): chlorthalidone 14; amlodipine 12; lisinopril 11.

Hazard ratios associated with subjects who developed DM2 vs those who did not develop DM2 during the first 2 years with subsequent cardiovascular disease:

	Chlorthalidone	Amlodipine	Lisinopril
CHD	1.46	1.71	2,23
Stroke	1.83	2.63	0.48
Heart failure	0.96	1.29	3.66
Combined cardiovascular disease	0.96	1.14	1.31
Total mortality	1.05	1.92	1.31

Although none were statistically significant, this suggests that outcomes in patients taking chlorthalidone may be more favorable than in patients taking the other drugs.

Conclusion: FG levels increase in older adults with hypertension regardless of the treatment type. Compared with the other drugs, chlorthalidone modestly increased the risk of FG above 125 mg/dL (DM) There was no conclusive or consistent evidence that this chlorthalidone-associated increase in DM increased risk of clinical events over 5 years.

I believe this is an important clinical point, well worth the time I spent studying and abstracting the article. I believe that judicious use of thiazides remain the cornerstone of treatment for hypertension. Start low and go slow (eg, up to 25 mg hydrochlorothiazide). I would add a second and third drug rather than increasing the dose of the thiazide.

There must have been two different types of DM in the chlorthalidone group: 1) That as a result of the drug, and 2) That which, as age of the cohort increased, occurred spontaneously – not related to the diuretic. The study concerned only group 1).

"Thiazides Become The Cornerstone"

11-6 NEW-ONSET DIABETES MELLITUS LESS DEADLY THAN ELEVATED BLOOD PRESSURE?

The evidence that thiazide therapy is effective for treatment of hypertension passes numerous standards, including pharmacological and mechanistic plausibility, robust outcomes in heterogeneous groups of patients, favorable results in head-to-head comparison with other agents, and efficacy in combination therapy trials.

In all stages of hypertension and in the elderly population, thiazide-based therapy significantly reduces risk of stroke, coronary events, congestive heart failure, renal failure, and malignant hypertension.

While the occurrence of new-onset DM is an independent predictor of cardiovascular risk, administration of diuretics is not independently associated with cardiovascular risk. The recent guidelines from the British Hypertension Society state: "It is not clear that an elevated blood glucose developing as a consequence of drug treatment has the same long-term health impact as in other circumstances."

"Indeed, evidence is mounting that diuretic-induced DM may be completely benign".

"This finding bolsters the concept that thiazide-induced DM is a different and benign disease entity compared with either do novo DM, or that which develops in the context of other antihypertensive agents."

ALLHAT found that thiazide was more effective in lowering BP than either CCB or ACE. We might conclude that the benefit of BP reduction outweighs any risk associated with development of DM.

"Viewed through the wide-angle lens of outcomes research, thiazides become the cornerstone on which blood pressure-lowering treatment should be built."

I believe the benefit / harm –cost ratio of judicious use of thiazides as a first-line drug for hypertension is higher than other antihypertension drugs.

ILLITERACY

Screening For Literacy May Become A New "Vital Sign".

7-1 ILLITERACY: The Silent Epidemic

A large survey conducted by the National Center for Education Statistics estimated that 14% of adults in the US have "below basic" level of "prose literacy", defined as the ability to use printed and written information in order to function in society, to achieve one's goals, and to develop one's knowledge and potential.

Adults with below basic skills have no more than the most simple literacy skills. They lack ability to read documents such as drug and food labels.

Survey results indicate that more than a third of English-speaking patients, and half of Spanish-speaking patients at US public hospitals have low health literacy.

People with low literacy are more likely to be in poor health, and are more likely to have diabetes, poorly controlled diabetes, and heart failure. They are often ashamed of their problem and are adept at hiding it.

Our vast medical literature presents studies which enter only literate subjects. We in primary care are usually the clinicians who meet non-literate patients.

Our patients may be literate in non-English languages. I believe more primary care clinicians should learn to speak basic Spanish—a beautiful language.

All the applications of modern medicine (advances in dietary and drug therapy) are useless if the patient cannot adhere to a prescribed regimen, whether it be due to lack of understanding, lack of will, lack of social support, or lack of financial means.

IMPAIRED FASTING GLUCOSE (See DIABETES)
IMPAIRED GLUCOSE TOLERANCE (See DIABETES)
INCRETIN MIMETICS (See DIABETES)

INFLUENZA

Vaccinating The Staff Protects The Residents

12-1 EFFECTIVENESS OF AN INFLUENZA VACCINE PROGRAMME FOR CARE HOME STAFF TO PREVENT DEATH, MORBIDITY, AND HEALTH SERVICE USE AMONG RESIDENTS.

Vaccination of residents of care-homes against influenza can be effective in preventing respiratory illness, admissions to hospital, and death. The immune response in the elderly, however, is reduced. Protection against flu is only 50% to 70%. Residents are vulnerable to flu outbreaks even when vaccination rates are high.

These investigators hypothesized that vaccination of the *staff* would reduce transmission to *residents*, and therefore reduce residents' influenza-like illness, and associated deaths and health service use.

Randomized controlled trial followed 44 large private-chain UK elder-care homes during 2 flu seasons—2003-04 and 2004-05 (Total residents = 2604; total staff = 1703.) All residents had been routinely offered flu vaccine. The homes had not routinely offered vaccination to staff members.

Randomized to: 1) intervention homes, and 2) matched control homes.

Vaccination for flu was offered to the staffs of the intervention homes, but not to control homes.

	Vaccine coverage of full time staff	Vaccine coverage of part-time staff
Intervention homes	48%	21%
Control homes	6%	4%

All-cause mortality was less in the residents of intervention homes by 5 per 100 residents. Consultations for flu-like illness 7 per 100 less in intervention homes. Admissions to hospital for flu-like illness less by 2 per 100.

Conclusion: Vaccinating the staff against influenza can prevent deaths, and lower health care service use and flu-like illness among the residents of elder-care homes.

The Healthcare Infection Control Practices Advisory Committee, and the Advisory Committee on Immunization Practices recommend influenza vaccination for health care personnel.

I do not know how the general health and age of "care home" residents in the UK compares with that of residents of "retirement homes" in the USA. Many elderly in the USA homes remain in good health and continue to be active. Most receive flu vaccine every year. Many residents are also receiving assisted care and nursing care. I would judge that, overall, immune response to flu vaccine is attenuated.

"This Result Was Somewhat Unexpected"

12-2 PREVENTION OF ANTIGENICALLY DRIFTED INFLUENZA BY INACTIVATED AND LIVE ATTENUATED VACCINES

The efficacy of flu vaccines may decline during years when the circulating viruses have antigenically drifted from those included in the vaccine.

The vaccine to be given later in the year 2004-05 was formulated in February of 2004. By the winter of 2004, the strains of circulating virus had antigenically drifted from the viruses included in the vaccine:

Vaccine	Nationally circulating virus
Type A/New Caledonia /20/99 (H1A1)	
Type A/Wyoming/3/2003 (H3N2)	Type A California/072004-like strain (H3N2)
Type B/Shanghai/361/2002-like strain (Yamagata lineage)	Type B Hawaii/33/2004-like strain (Victoria lineage)

This study determined efficacies of both the traditional killed vaccine and the newer attenuated live vaccine and compared them with placebo in preventing symptomatic, laboratory confirmed flu.

Immune response to vaccine was much more robust for the killed vaccine.

Efficacy favored the killed vaccine.

Absolute difference (%) between killed vaccine and placebo:

For types A and B combined	5.5 %	NNT = 18 *
For type A	3.1 %	NNT = 32

Absolute difference (%) between live vaccine and placebo:

For types A and B	2.4 %	NNT = 42
For type A	2.1%%	NNT = 48

(* Number of subjects needed to treat to prevent one laboratory-confirmed case of flu.

My calculations from their data RTJ)

Absolute difference (%) between killed vaccine and placebo:

For type B	2.8 %	NNT = 47

Absolute difference (%) between live vaccine and placebo:

For type B	1.7%	NNT = 59

In the year 2004-05 when antigenically drifted type A (H3N2) influenza and an additional type B virus were circulating, the killed vaccine worked well. “This result was somewhat unexpected, given the problems reported in past years when antigenically drifted viruses were circulating.”

The live attenuated vaccine appeared to be protective, particularly against type A influenza, although the absolute efficacy estimates were not (*statistically*) significant.

Conclusion: In the 2004-2005 flu season, when most circulating viruses were dissimilar to those included in the vaccine, the killed vaccine was efficacious in preventing laboratory confirmed symptomatic influenza in healthy adults. The live attenuated vaccine was less efficacious.

This certainly suggests that we should provide vaccine for everyone every year. Even if the virus and the vaccine do not match, the killed vaccine may provide some protection in adults. This news is encouraging as we enter the era of universal vaccination against flu. Note that the general type H3N2 did not drift. I wonder if vaccine would give any protection if the drift were greater, and a completely new viral type became epidemic (eg, H5N1). I doubt it. The news about the attenuated live vaccine is not reassuring, at least for adults.

See the following abstract concerning children.

Evidence Of A Herd Immunity Effect

12-3 EFFECTIVENESS OF SCHOOL-BASED INFLUENZA VACCINATION

Children are important vectors for the spread of influenza. Focusing efforts on flu vaccination of healthy children may be an effective and practical method of reducing the burden of flu in the *community*.

This study assessed the effect of a school-based vaccination program on *households* of children attending schools. (A herd immunity effect.)

Selected 11 intervention schools (total students = 5840; mean age = 8) and 17 matched control schools (total students = 9451) in 4 states representing geographically and demographically diverse regions. Offered live attenuated vaccine at no charge to all healthy children age 5 years and older in the intervention schools.

Outcomes:	Intervention schools	Control schools	Absolute difference (Adjusted)
Children %			
Any fever or flu-like illness	40	52	11
Fever + cough or sore throat	17	26	8
Adults in households %			
Any fever or flu-like illness	32	44	11
Fever + cough or sore throat	8	13	4

Conclusion: Incidence of flu-like illness was lower in households of children who received the live attenuated vaccine than households of children who did not receive the vaccine.

The study is provocative, not definitive. "Flu-like illness" is not necessarily influenza.

Note the benefit was evident despite an antigenic drift. (See the previous abstract.)

This is another indication that more generalized use of flu vaccines can promote "herd" immunity.

INHALED INSULIN (See DIABETES)

INSULIN (See DIABETES)

INTERMITTENT CLAUDICATION

"An Important Warning Signal To Start Measures To Reduce Risk Of Cardiovascular Events"

11-9 INTERMITTENT CLAUDICATION A *Clinical Review*

In the vast majority of cases of IC, atherosclerosis is the underlying pathology.

Patients with peripheral arterial disease have the same risk of death from cardiovascular causes as those with a history of coronary or cerebrovascular disease.

Cigarette smoking is by far the most potent risk factor. Other risk factors are age, diabetes, hypertension, dyslipidemia, and hyperhomocysteinemia.

Early diagnosis and risk factor control by primary care clinicians is critical in reducing the mortality associated with IC.

Primarily, treatment should be targeted at reducing factors for atherosclerosis risk of cardiovascular events through secondary prevention (smoking cessation, hypertension control, statin drugs, antiplatelet drugs, diabetes control). Secondarily, treatment should aim to improve symptoms.

Regular exercise, at least 3 times a week, has been shown to improve walking distance and maximal exercise time.

The work "peripheral" may explain why the importance of the disease as a manifestation of general

atherosclerotic disease. IC should not be seen as “peripheral”, but as an important “central” warning signal to start measures to reduce risk of cardiovascular events. Primary care doctors have a major role in prevention of cardiovascular complications.

IRON DEFICIENCY (See ANEMIA)

KIDNEY FUNCTION (See CYSTATIN C)

LIFESTYLE INTERVENTION (See DIABETES)

LIVER FAILURE

“Might Be Associated With Exaggerated Liver Injury In Some Individuals.”

12-9 PARACETAMOL (ACETAMINOPHEN; *TYLENOL*); *Are Therapeutic Doses Entirely Safe?*

Acetaminophen (eg, *Tylenol*) is thought to be safe in recommended doses (up to 4 grams daily in adults). It is currently the most widely used analgesia and antipyretic drug worldwide.

It is hepatotoxic and nephrotoxic at doses greater than 4 g a day. It has become an important cause of acute liver failure. The most severe cases may require liver transplant. Mortality may be high.

In recent years, unintended overdoses, rather than those that are intentional, have been the main cause of acetaminophen-induced acute liver failure in the USA. The dose leading to liver failure may be as low as 7 grams a day.

A recent study was designed to determine why abnormal liver function tests were observed during studies of clinical development of a new combination of an opioid (hydrocodone) and acetaminophen. Participants were randomly assigned to placebo, acetaminophen-alone 4 g a day, or a combination of 4 g acetaminophen with one of three opioids. Duration of observation = 14 days. Although trough acetaminophen concentrations did not exceed therapeutic limits in any group, up to 44% of participants in the acetaminophen groups (including those given acetaminophen alone) had concentrations of alanine aminotransferase (ALT) more than three times the upper limit of normal (suggesting liver injury). No participant given placebo had an increase to this level. In 27% of participants ALT levels were increased to more than 8 times normal. The investigators concluded that the acetaminophen content was associated with ALT elevations.

Concomitant administration of opioids did not seem to increase ALT levels.

Awareness of possible toxicity is particularly important for people who are likely to be at high risk for hepatotoxicity—those dependent on alcohol, chronic users of acetaminophen, the severely malnourished, smokers, and those with acute liver disease.

I believe this is a valid clinical point. Primary care clinicians should be alert to possible acetaminophen toxicity. Note the rapid development of transferase elevations (within 14 days). I wonder—Why, considering the vast usage of acetaminophen, has this toxicity not been reported and disseminated before? My Goodman and Gilman "Pharmacological Basis of Therapeutics" does not mention liver toxicity from usual doses of acetaminophen, only from excessive doses.

Prevalence of impaired liver function is high in the US. This includes many elderly persons otherwise in good health..

The prevalence of non-alcoholic steatosis and steatohepatitis is increasing with the obesity epidemic. Are these patients more susceptible to toxic effects of acetaminophen?

LOW CARBOHYDRATE SCORE (See CORONARY HEART DISEASE)

LUNG CANCER

Should Primary Care Clinicians Advise Screening For Their High-risk Patients?

10-9 SURVIVAL OF PATIENTS WITH STAGE I LUNG CANCER DETECTED ON CT SCREENING

Screened over 31 000 asymptomatic persons (age 40 to 86) at high risk of lung cancer (**LC**)—the great majority because of a long smoking history (median 30 pack-years).

At the first screen, CT was positive for at least one non-calcified nodule in 13%. Of these, further study (including follow-up CT and biopsy) revealed cancer in 10%. The overall presence of cancer was 1.3% of the entire first-screen cohort.

Over 27 000 subjects negative for LC on the first screen then underwent annual CTs. In this cohort, the CT was positive for a non-calcified nodule in 5%. Of these 5% were cancerous (0.3% of the 27 000).

The investigators *estimate* that the 10-year LC-specific survival for subjects with stage I LC undergoing resection within one month of diagnosis is 92%.

In the investigator's opinion, screening is cost effective, and is similar to the cost effectiveness of mammography.

Conclusion: Annual spiral CT screening for persons at high risk of LC because of smoking can detect LC that is curable.

This observational study does not determine the actual survival rate of patients screened and operated on for stage I LC vs subjects with stage I LC not operated on. The stated benefits in terms of survival are estimates. No randomized, controlled trial will be done to clarify this point.

The study does place some responsibility of primary care clinicians. It raises interesting questions:

1) Should primary care clinicians now routinely advise screening for their high risk patients? (As we do for mammography.) Or should we defer consideration until the patient raises his desire for screening?

2) In any case, we should consider the age and co-morbidities of the individual patient before going on to screen. As with prostate cancer, older patients may die of other causes.

3) If we advise screening, must we insist that the patient stops smoking, and require proof of cessation?

An imaginary scenario:

Doctor to patient: "You are now 60 years old. You have been smoking a pack of cigarettes daily for 40 years. You have no symptoms suggesting lung cancer. If you undergo screening, the chances of finding a suspicious nodule on the first screen are about 1 in 10. If such a nodule is found, you will be asked to enter a protocol with follow-up CT scanning and likely a biopsy. The chance of having a biopsy which shows lung cancer is 2%. There is then a 15% chance that the cancer will be too far advanced to operate on with any chance for cure.

Investigators estimate that, overall, 92% of patients detected by screening, and operated on within one month will survive for 10 years. But, there is no way of telling if the surgery will 'cure' you, or whether it will prolong your life. If you are not operated on, it is highly likely that you will die of the cancer.

If you do not stop smoking, the chance of recurrence of the cancer is high. I believe your best option is to stop smoking immediately."

MACULAR DEGENERATION

"MIRACULOUS"

10-3 A VERY EFFECTIVE TREATMENT FOR NEOVASCULAR MACULAR DEGENERATION

Age related macular degeneration is a complex disorder which begins decades before a patient becomes symptomatic. In about 10% of patients with the condition, a derangement of vasculature beneath Bruch's membrane leads to a new growth of blood vessels from the capillaries beneath the membrane into the subretina. This neovascular complication damages the retina. It is responsible for the vast majority of cases of legal blindness attributable to this disease.

Vascular endothelial growth factor (VEGF; a protein) has emerged as an important molecule in the angiogenic process. Several recombinant monoclonal antibodies (ranibizumab is the latest FDA approved drug) have been designed to inhibit action of this growth factor. Patients receiving intra-*vitreous* injection of ranibizumab monthly over 2 years gained, on average, more than one line of visual acuity. Controls lost vision. Ranibizumab was much more effective than photodynamic therapy.

The efficacy of this treatment has been termed "miraculous".

While this application is not directly applicable to primary care, primary care clinicians should be aware of it.

Should We Give An Off Label Drug When The Patient Cannot Afford The Approved Drug?

10-4 RANIBIZUMAB, BEVACIZUMAB, AND TREATMENT OF MACULAR DEGENERATION—THE PRICE OF SIGHT

Ranibizumab (*Lucentis*; Genentech) is a fragment of a recombinant monoclonal antibody that binds to, and inhibits, vascular endothelial growth factors in and beneath the retina. It is injected into the vitreous monthly. Treatment is likely to be required indefinitely It presently costs about $2000 for a single dose.

A precursor recombinant antibody, bevaci-zumab (*Avastin;* Genentech), given intravenously, has been approved for treatment of metastatic cancer of the colon and rectum. It is now being given intravitreously (off label) in smaller doses at a much lower cost. It has not yet been directly compared with ranibizumab. The benefit/harm ratio compared with ranibizumab is not known. The cost differential is important.

MEDITERRANEAN DIET

The Healthy Diet Is Not A Low Fat Diet, It Is A Selected Fat Diet.

7-3 EFFECTS OF A MEDITERRANEAN-STYLE DIET ON CARDIOVASCULAR RISK FACTORS

Incidence rates of cardiovascular disease **(CVD)** have marked geographical differences. One factor may be diet. High adherence to the Mediterranean diet **(MD)** is associated with a reduction in mortality. The diet may also be associated with a reduced BP and improved lipid profiles.

Olive oil, a rich source of mono-unsaturated fatty acids is a main component of the MD.

Frequent nut intake has been associated with a decrease in rates of CVD.

This study randomized subjects to one of 3 diets:

1) Low fat diet: Subjects were advised to reduce intake of all types of fat. They were given a leaflet describing the American Heart Association recommendations. Diet was similar to the DASH diet.
2) MD with added olive oil: Participants were given one liter of olive oil to consume each week.
3) MD with added nuts: Participants were given sachets of nuts to take 30 g / day.

Compared with the low fat diet, the 2 MDs produced beneficial changes BP, fasting glucose, insulin levels, and lipids. Not much difference between olive oil and nut groups.

The diets (except for olive oil and nut content) were similar to the DASH diet which is associated with lowering of BP. The authors state that if salt were restricted (as in the low sodium DASH diet) BP would likely be lowered still more.

Compared with a low-fat diet (similar to the DASH diet), a MD supplemented with virgin olive oil or nuts had beneficial effects on cardiovascular risk factors.

I would assume that a combination of olive oil and nuts would produce the same benefits, and would be easier to adhere to. Why not consider other mono-unsaturated oils (peanut; canola) beneficial as well? They may be less expensive than olive oil.

For prevention of CVD, the "low-fat" diet is no longer considered the most beneficial. The most beneficial diet is a moderately high mono-unsaturated fat, very low saturated fat; no trans fat diet.

I believe poly-unsaturated fats may be substituted for mono-unsaturated fats and produce similar benefits. Some would add low-salt and low glycemic load to the diet.

The added nut and olive oil diet would likely increase weight over time. If one adopts these diets, energy intake must not be increased. This may be difficult for individual patients.

For patients and physicians who are interested in a detailed description of the MD go to:

www.postgradmed.com/issues/2002_02/curtis.htm Accessed August 28, 2006

Google also presents a variety of information.

METHICILLIN-RESISTANT *S. aureus* INFECTIONS

"The Most Common Identifiable Cause Of Skin And Soft Tissue Infections"

8-6 METHICILLIN-RESISTANT *S. aureus* INFECTIONS AMONG PATIENTS IN THE EMERGENCY DEPARTMENT

Methicillin-resistant *Staphylococcus aureus* (**MRSA**) emerged in the 1960s as a cause of infection among persons exposed to the bacteria in health care settings. More recently MRSA have been reported among persons without such exposure. (Community-associated MRSA [**CA- MRSA**]).

There has been a dramatic trend of increased prevalence of CA-MRSA in the past few years. It has emerged as the most common identifiable cause of skin and soft tissue infections.

As compared with health-care associated MRSA, CA-MRSA isolates tend to be sensitive to more antibiotics and to produce different toxins. They have different types of the gene complex which confers methicillin resistance.

This prospective prevalence study involved community-dwelling adults (median age 39; 2/3 male) with skin and soft tissue infections presenting to hospital EDs in 11 different U.S. cities during one month in 2004. All were age 18 and over; all had purulent skin and soft tissue infections of less than one week's duration.

MRSA was isolated from 59% of all patients. It was the most common identifiable cause. All were sensitive to trimethoprim-sulfamethoxizole and rifampin.

In 100 of 175 MRSA infections for which antibiotics were provided, 57% were *not* concordant with results of susceptibility testing.

At day 17 after the ED visit, 96% of patients reported that their infection had resolved or improved. There was no difference in outcome between those infected with CA-MRSA and those infected with other bacteria, or between those whose CA-MRSA was resistant and those whose CA-MRSA was sensitive to the antibiotic prescribed.

There was no association between patient's outcomes and susceptibility of the organism to the antimicrobial used. This suggests that most CA-MRSA infections can be cured with adequate drainage. The susceptibility of a given pathogen to prescribed antimicrobial agents may be more likely to affect the outcome among patients with cellulitis or purulent wounds.

CA-MRSA is the most common identifiable cause of skin and soft tissue infections in community-dwelling patients presenting to EDs. Clinicians should consider obtaining cultures and modifying empirical therapy to provide CA-MRSA coverage.

It seems to me that the problems are: staph are ubiquitous, the carrier rate is high, and the tendency to mutate is also high. This leads to recurrent and changing antibiotic resistance. Distinguishing hospital acquired infections from community acquired infections, I believe, is arbitrary. Our challenge is to be ever vigilant for mutations, and

to keep up with the antibiotic-resistant and sensitive profile. .Meanwhile application of traditional sanitary methods of reducing likelihood of spread of the infection remains paramount.

"Potentially Pose A Nightmare Scenario"

8-7 THE TREATMENT TRIANGLE FOR STAPHYLOCOCCAL INFECTIONS

New community-acquired methicillin-resistant *Staphylococcus aureus* (**CA-MRSA**) are highly virulent. They cause skin and soft-tissue infections and necrotizing pneumonia in otherwise healthy adults and children. (*Hospital acquired MRSA are even more virulent and deadly*.)

Acquisition of novel genetic elements confer a selective advantage in growth and survival of some CA-MRSA strains. They may be well adapted to skin colonization thereby allowing them to establish and maintain cutaneous colonization more effectively. "Such strains potentially pose a nightmare scenario in which routine low-virulence cutaneous staphylococci are replaced by aggressive MRSA." Outbreaks have already been described in association with overcrowding and close person-to-person contact.

Antibiotic susceptibility of CA-MRSA varies. This susceptibility highlights the need for culture in order to guide treatment after empirical antibiotic therapy is begun.

In the study, the great majority of patients were treated with incision and drainage. This was associated with a good long-term outcome. The clinical management of skin and soft tissue infections has returned to the basic principles. The editorialist proposes a triangle of treatment options:

1) Drainage and debulking
2) Wound culture
3) Antibiotic therapy

The weight is on drainage and debulking.

Basic practices such as separation of infected patients, routine cleaning of shared equipment, and appropriate hand hygiene are being rediscovered.

MICROCYTIC ANEMIA (See ANEMIA)

MIGRAINE

POUNDing Migraine is a Symptom Complex

9-4 DOES THIS PATIENT WITH HEADACHE HAVE MIGRAINE OR NEED NEUROIMAGING?

In assessing patients with headache (**HA**), clinicians are often faced with two important questions. Is the HA migraine.? Does the patient require neuroimaging?

Patients who present with classic visual aura—a slowly evolving scintillating scotoma that moves or passes through the visual field over roughly 30 minutes, then disappears, and is followed by the onset of unilateral disabling HA—constitute an easy diagnosis.

The study suggests 5 questions used as a screening tool for migraine without aura:

1) Is the HA pulsating?
2) Does it last between 4 and 72 hours (without medication)?

3) Is it unilateral?

4) Is nausea present?

5) Is the HA disabling?

If the answer is "yes" to 4 or 5, the likelihood ratio of migraine is high (LR = 24: migraine *vs* not-migraine). If 3 are present, LR is 3.5. For 1 or 2, the LR is below 1.0

These authors have constructed a mnemonic based on these 5 criteria: POUNDing

P = PULSATING

hO = HOURS OF DURATION (4 to72)

U = UNILATERAL

N = NAUSEA OR VOMITING

D = DISABLING

Looking for a *combination* of symptoms is important in the diagnosis of migraine.

Neuroimaging is more likely to reveal intracranial pathology if the HA is associated with:

1) An abnormal neurological examination.

2) A thunderclap HA

3) Atypical aura

4) Altered mental status

5) Associated pathology: cancer; HIV infection.

NON-ALCOHOLIC STEATOHEPATITIS

A 'Proof of Concept': Pioglitazone Efficacious In Patients With Nonalcoholic Steatohepatitis."

11-7 A PLACEBO-CONTROLLED TRIAL OF PIOGLITAZONE IN SUBJECTS WITH NON-ALCOHOLIC STEATOHEPATITIS

Non-alcoholic steato-*hepatitis* (**NASH**) is characterized by: insulin resistance, accumulation of hepatic fat, and a predominantly lobular necro-inflammation of the liver. It may or may not include centrilobar fibrosis. It may progress to cirrhosis. It is commonly associated with type 2 diabetes (**DM2**) and obesity.

Thiazolidinediones may reverse many of these abnormalities by ameliorating insulin resistance in adipose tissues, in the liver, and in muscles. They increase adiponectin levels in the plasma, stimulate fatty acid oxidation, and inhibit hepatic fatty acid synthesis. They also have anti-inflammatory effects.

This study followed 55 patients (mean age 51; BMI 33). All had a liver biopsy. All had histological features of NASH. All had impaired glucose tolerance or DM2, increased plasma insulin levels, increased plasma free fatty acids, and increased hepatic fat content (assessed by MRI).

Randomized to: 1) a hypocaloric diet + pioglitazone 45 mg daily, or 2) a hypocaloric diet + placebo

Subjects with NASH who received pioglitazone for 6 months had improved insulin sensitivity, a reversal of

the metabolic milieu permissive of steatosis of the liver, and amelioration of cytokine-mediated systemic inflammation (tumor necrosis factors). Also had improved hepatic insulin sensitivity and glucose clearance, reductions in plasma free fatty acids, plasma glucose, and insulin levels

The histological features of steatohepatitis (steatosis, ballooning necrosis, and centrilobular inflammation) also improved.

Read the following editorial

"The Most Common Form Of Chronic Liver Disease"

11-8 THIAZOLIDINEDIONES FOR NON-ALCOHOLIC STEATOHEPATITIS—PROMISING, BUT NOT READY FOR PRIME TIME

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

Nonalcoholic fatty liver disease is the most common form of chronic liver disease. It begins with hepatic steatosis, an accumulation of excess fat in hepatocytes. Steato*hepatitis*, the most severe form of the disease, develops in about 5% of patients with steatosis.

The prognosis of steato*hepatitis* is poor, rivaling that of hepatitis C. Once it develops, many patients will die of liver-related causes (cirrhosis, hepatocellular cancer, and liver failure).

Thiazolidinediones are more effective treatment than metformin. (Although a recent study reported that rosiglitazone was of little benefit.) Unfortunately thiazolidinediones may be associated with weight gain. The author suggests adding the two drugs as first treatment of nonalcoholic fatty liver disease in patients with type 2 diabetes. The combination may provide the same benefits as thiazolidinedione alone, and may avoid the weight gain associated with thiazolidinediones.

Many other approaches to treatment of hepatic steatosis and steatohepatitis have been proposed. None, except bariatric surgery has changed the natural history

Nevertheless, "Until results of large controlled studies of at least one to two years are available, dietary modification, exercise, and treatment of co-existent conditions should be the preferred strategy for managing nonalcoholic steatohepatitis." *(Although I believe the author would agree that this strategy has little chance of success in most obese patients. RTJ)*

Thiazolidinediones are an approved therapy for DM2. If a patient with DM2 is obese (BMI > 30), I believe it would be reasonable to include pioglitazone therapy for the DM2, expecting it to improve any associated hepatic steatosis-steatohepatitis. I believe it is reasonable to combine it with metformin.

OBESITY

Overweight (BMI 25 To 30) is Associated With Increased Risk Of Death.

8-3 OVERWEIGHT, OBESITY, AND MORTALITY IN A LARGE PROSPECTIVE COHORT OF PERSONS 50 TO 71 YEARS OLD.

Epidemiologic evidence indicates that obesity, defined by a body mass index (**BMI**) of 30 or more is associated with increased risk of death.

Is overweight (BMI 25.0 to 29.9) also associated with increased risk? A substantial proportion of the adult population is overweight, but not obese.

This National Institutes of Health study examined the association between BMI and risk of death based on a cohort of over ½ million people age 50-71 at baseline. The cohort was large enough to permit minimization of potential bias caused by preexisting disease and smoking.

Men: A subgroup of men who had never smoked, based on BMI at age 50: (n = > 55 000; > 4000 deaths)

A. The lowest relative risk of death (RR = 1.00) occurred between BMI 22.5 and 24.5

B. The relative risk (RR) of death increased as BMI rose:

	BMI 22.5 to 25	25 to 30	30 to 40
Relative risk of death	1.00 (referent)	1.8	2.8

C. RR *rose* slightly in men with a BMI *under* 22.5. [The investigators did not comment on any possible reason.]

Women: A subgroup of women who had never smoked, based on BMI at age 50: (n = > 55 000; > 4000 deaths)

A. The lowest relative risk of death (RR = 1.00) occurred between BMI 19.0 and 24.0

B. The relative risk (RR) of death increased as BMI rose:

	BMI 19.0 to 24.0	24 to 30	30 to 40
Relative risk of death	1.00 (referent)	1.4	2.8

C. RR rose slightly in women with a BMI *under* 19.

Excess weight accounted for approximately 18% of all premature deaths in men who had never smoked, and 19% of premature deaths among women who had never smoked.

Conclusion: Being overweight (BMI 25 to 30) is associated with an increased risk of death.

This is a much more detailed study than I have indicated. It presents many tables and baseline characteristics.

"The Diagnosis Of Obesity Is Rarely Recorded"

9-1 OBESITY—*Time To Wake Up*

"An evidence-base of effective measures for preventing obesity does not exist."

"Obesity does not need a scientific breakthrough to be treated successfully."

"In practice, height and weight are often not recorded. The diagnosis of obesity is rarely recorded. BMI is seldom measured in persons of normal weight. Thus, progression to overweight is missed, and with it the opportunity to prevent more than half of the burden of diabetes."

"The metabolic and vascular benefits of even modest reductions in weight are well described. The most striking benefits, in proportional terms, are from modest weight loss (5% to 10%), when fat is particularly lost

from intra-abdominal sites. This amount of loss increases life expectancy an average of 3 to 4 years for overweight patients with type 2 diabetes."

Read the full abstract for more clinical points.

I believe our number one goal of primary care should be making all persons take responsibility for their own health and well-being by adopting healthy habits.

Some primary care clinicians have a weight problem. This may deter them from confronting obese patients about their problem.

Some clinicians may be discouraged about advising obese patients because of a perceived lack of effectiveness of treatment.

I can think of no more simple, no-cost, and potentially valuable measure to reduce risk of disease than weight loss.

If only it were not so difficult!

Waist Circumference—A Simple, No Cost, Valid, And Important Marker of Risk.

9-2 OBESITY: Body Mass Index and Waist Circumference

"The main difficulty with anthropometric measures is that doctors and the public are not aware of the value of these measures. More sophisticated and expensive measurements are no better for determining body fat."

"Waist circumference was developed originally as simpler measure—and a potentially better indicator of health risk than BMI. It is at least as good an indicator of total body fat as is BMI. It is the best predictor of visceral (intra-abdominal) fat and total fat."

"The most clinically telling physical sign of serious underlying disease is increased waist circumference, which is linked to insulin resistance, hypertension, dyslipidemia, a pro-inflammatory state, type 2 diabetes, coronary heart disease, sleep apnea, and gallbladder disease."

"Abdominal (visceral) fat is metabolically active."

Read the full abstract for other clinical points.

Primary care clinicians should chart waist circumference and BMI.

Obesity Drugs Can Increase Weight Loss By About 4 To 6 Kg Above What Can Be Achieved By Diet Alone.

10-1 OBESITY—DRUG TREATMENT

"Despite the availability of evaluated and approved obesity drugs, and even though some patients will have failed to lose weight after non-drug treatment—doctors have been reluctant to prescribe drugs." This may because of memories of past adverse effects of amphetamine and amphetamine-like drugs.

The use of obesity drugs should follow the principles of any other therapeutic area—that is, they may be prescribed after assessment of the potential benefits and risks (both clinical and economic).

Effective treatment, including drugs when needed, must be life long and focused on maintenance of weight loss in a similar fashion to the effective treatment of hypertension and diabetes. Drugs are logical treatment, not just for weight loss induction, but for long term weight loss maintenance.

Overall benefits of existing drugs has been favorable in terms of symptoms, risk factors, and diabetes prevention.

The review discusses two obesity drugs: orlistat and sibutramine.

Read the full abstract.

I believe vitamin supplementation should be prescribed for patients attempting to lose weight, including those on drugs.

"The Safety And Efficacy Of Surgery Has Improved Remarkably"

10-2 OBESITY MANAGEMENT – SURGERY

Obesity surgery ("bariatric", or "behavioral" surgery) is a successful validated, and legitimate treatment and needs to be considered in some circumstances."

Twelve clinical points. Read the full abstract

OPIATES (See ABDOMINAL PAIN)

OSTEOPOROSIS

Continued Treatment For An Additional 5 Years Increased BMD

12-7 EFFECTS OF CONTINUING, OR STOPPING, ALENDRONATE AFTER 5 YEARS OF TREATMENT The FLEX Trial

Alendronate (*Fosamax; Merck*) is a potent bisphosphonate which decreases bone turnover, increases bone mineral density (**BMD**), and decreases risk of fracture in women with osteoporosis. The optimum duration of treatment of women with postmenopausal osteoporosis is uncertain.

This study compared the effects of discontinuing alendronate after 5 years vs continuing for 10 years. (At baseline, all had received alendronate for 5 years.)

Randomized 1100 postmenopausal women to: 1) alendronate 5 mg daily; 2) 10 mg daily, or 3) placebo. (The study combined outcomes of 5 and 10 mg because there were small BMD differences noted between them.)

Mean change in BMD after an additional 5 years:

	Placebo (%)	Combined 5 mg and 10 mg (%)
Total hip	-3.38	-1.02
Femoral neck	-1.48	+0.46
Trochanter	-3.25	-0.08
Lumbar spine	+1.52	+5.26
Total body	-0.27	+1.01

Those who continued alendronate had a statistically significant lower risk of clinically recognized vertebral fractures (2.4% for alendronate vs 5.3% for placebo).

No significant differences between groups for serious adverse events, including upper g.i. events.

Conclusion: Compared with 5 years of therapy, continuation of alendronate (either 5 or 10 mg daily) for a total of 10 years maintained BMD and reduced bone remodeling. The risk of clinically evident vertebral fractures was lower in those who continued alendronate.

Practical Pointers has abstracted many studies about osteoporosis. All have reported the effects of drugs on patients with established osteoporosis—ie, treatment of the disease, not prevention. I await a study which begins treatment at menopause (likely with low dose bisphosphonates + calcium and vitamin D supplements) to prevent or retard development of osteoporosis. I judge this would be a more effective clinical method to prevent the devastating effects of osteoporosis much more effectively than treatment after osteoporosis has developed.

OVERACTIVE BLADDER

11-10 TOLTERODINE AND TAMSULOSIN FOR TREATMENT OF MEN WITH LOWER URINARY TRACT SYMPTOMS AND OVERACTIVE BLADDER

Overactive bladder syndrome (**OABS**) is characterized by urinary urgency, and increased frequency during the day and night—with or without incontinence. An estimated 10 million men over age 40 have symptoms consistent with OABS. The symptoms are often attributed to detrusor overactivity, characterized by involuntary detrusor contractions during bladder filling. Detrusor overactivity may co-exist with bladder outlet obstruction due to benign prostatic hyperplasia (**BPH**)[1].

The resultant increased pressure leads to structural changes in the bladder, which in turn increases the excitability of detrusor smooth muscle. Outlet obstruction may cause urinary hesitancy, intermittency, weak stream, and other lower urinary symptoms.

This randomized, double-blind, placebo-controlled trial followed 879 men (mean age 62). All had documented symptoms of overactive bladder with 8 or more micturations daily, and urgency symptoms 3 or more times daily, with or without incontinence.

Randomized to: 1) tolterodine ER (*Detrol ER* 4 mg daily; blocks the muscarine receptor of acetylcholine;) 2) tamsulosin (*Flomax* 0.4 mg daily; blocks adrenergic action on the prostate smooth muscle), 3) both together, or 4) placebo. Follow-up for 12 weeks:

	Placebo	Tolterodine ER	Tamsulosin	Both
Treatment benefit (%)	62	65	71	80

(In absolute terms, the difference between placebo and two drugs combined was 18%; NNT to benefit one patient = 6.)

Conclusion: Treatment with combined tolterodine ER + tamsulosin resulted in clinically significant benefit for men with moderate to severe lower urinary tract symptoms.

Primary care clinicians might choose to prescribe one drug to test its benefit, and add the second drug if response is not satisfactory.

OVERWEIGHT (See OBESITY)

PAIN (See ABDOMINAL PAIN)
PIOGLITAZONE (See NON-ALCOHOLIC STEATOHEPATITIS)
"POLYPILL" (See DIABETES)
POST-INFECTIVE FATIGUE SYNDROME

PRIMARY CARE MEDICINE

"The Backbone of the Nation's Health Care System" is in Trouble

8-1 PRIMARY CARE—WILL IT SURVIVE?

The American College of Physicians recently warned, "primary care **(PC),** the backbone of the nation's health care system, is at grave danger of collapse". "Indeed, primary care is facing a confluence of factors that could spell disaster."

Fewer U.S. medical graduates are choosing careers in PC .

Many primary care physicians **(PCPs)** are unhappy with their jobs. The editorialist lists a number of reasons: 1) Increasing demands. 2) More difficulty in communication. 3) Insufficient reimbursement.
In addition, patients are expressing frustration about primary care service.

The editorialist has presented some problems, but, I believe, has overstated.

I have long maintained that primary care is the most difficult specialty to perform well and, despite being the most demanding, is the most gratifying.

In order to function more efficiently, PCPs must have a close relationship to their specialist consultants. They should know them personally and understand their capabilities and limitations. They should be able to call on them freely and on a timely basis.

PCPs must also have a working relationship with other health care workers in the community: public health departments, social services, pharmacists. PCPS must work in teams They must place greater reliance on nurse practitioners. I believe that nurse practitioners can serve with competence and can work efficiently with primary care clinicians. It may be that more communities will begin to rely on them.

Increased computer use may help.

I do believe that the efficiency of medical care in the U.S. would improve if more PCPs were available and distributed evenly. Increased pay and decreased patient load are unlikely to occur and by themselves are not likely to solve all problems.

For a different view, see the following abstract.

8-2 PRIMARY CARE—The Best Job In Medicine?

(This editorialist comments on some of the positive aspects of PC.)

"Taking care of patients as their primary care doctor is the best job in medicine."

It is a privilege to be a physician and to gain the trust of patients. Becoming an accomplished primary care clinician is a life-long quest.

Read the full abstract.

PROTON PUMP INHIBITOR

Associated With An Increase In Hip Fracture.

12-8 LONG-TERM PROTON PUMP INHIBITOR THERAPY AND RISK OF HIP FRACTURE

Millions of people are taking PPIs continuously, and long –term. PPI use leads to hypochlorhydria, particularly among elderly people who may have decreased PPI clearance. Hypochlorhydria could lead to calcium malabsorption, low bone mineral density, and increased risk of fracture.

This case-control study compared users of PPI and non-users, all over age 50.

Cases—patients with incident hip fracture (n = 13 556).

Controls—matched to cases (n = 135 000).

Compared PPI use in cases vs controls. Main outcome = risk of hip fracture associated with PPI use.

The adjusted odds ratio for hip fracture associated with more than 1 year of PPI use was 1.4.

The strength of the association rose with duration of PPI use:

PPI use	1 year	2 years	3 years	4 years
Odds ratio	1.2	1.4	1.5	1.6 (Adjusted for some possible confounders)

The risk of hip fracture was markedly increased among *long-term* users of *high-dose* PPI as compared with non-users of acid-suppression. (Odds ratio = 2.7)

Gastric acid may be important for absorption of insoluble calcium. Calcium malabsorption secondary to acid suppression by PPI therapy may potentially explain the association.

Conclusion: Long-term PPI therapy, particularly at high doses, was associated with an increase in hip fracture.

I believe this is a valid clinical point. Patients fitting these criteria should receive calcium and vitamin D supplementation long-term, and more liberal recommendations for use of bisphosphonates.

PSA SCREENING

Inappropriate Screening Is Common Among The Elderly.

11-2 PSA SCREENING AMONG ELDERLY MEN WITH LIMITED LIFE EXPECTANCIES

Most guidelines do not recommend PSA screening for prostate cancer (**PC**) in elderly men with limited life expectancy. The potential harms, which occur immediately, outweigh potential benefits. Potential harms

include: additional procedures due to false positive results, psychological distress, and morbidity associated with treating clinically insignificant PC.

The American Urological Society recommends annual PSA screening for men over age 50 and older if they have more than a 10-year life expectancy, usually defined as having a greater than a 50% probability of surviving 10 years. The US Preventive Services Task Force concluded that evidence is *insufficient* to recommend *routine* PSA screening, and that men with a low probability of surviving 10 years are unlikely to benefit from screening, even under favorable assumptions.

"All agree that currently there is no conclusive evidence that PSA screening reduces prostate mortality at any age or life expectancy, and convincing evidence of benefit is unlikely to ever exist for elderly men because ongoing randomized trials of PSA screening have excluded men older than 75 years."

This cohort study of over 550 000 male veterans age 70 and older (median age = 77) seen in Veterans Affairs
facilities in 2003. None had a history of PC, elevated, PSA, or symptoms of PC.

In 2003, 56% of these elderly men received a PSA test.

Screening decreased with advancing age within each 5-year age group, ranging from 64% in men age 70-74 to 36% in men age 85 or older.

The percentage of men who received PSA screening did not substantially decline with worsening health. (Eg, among men age 85 and older, 34% in best health had a PSA compared with 36% of those in worst health.)

There is strong evidence that few men age 70 or more who are in the poorest health due to co-morbidity will survive 10 years. Yet 51% of these men were screened with PSA.

Conclusion: PSA screening among elderly veterans with limited life expectancy should be much lower, given the known harms of screening. More attention to prognosis is needed when recommending screening for elderly men.

This advice extends to other screening and interventions. Like an expert poker player, the expert clinician should know "When to hold and when to fold". When should we stop colonoscopy? Lipid screening? Routine physical examinations? Mammography? Pelvic examinations and Pap Smears? When should we stop some of the many multiple drugs old patients take?

How should we respond when an elderly patient requests screening?

I believe, as primary care clinicians, we sometimes order a screening procedure (especially PSA) without adequately informing the patient about potential harms as well as benefits.

RADIATION ALARMS IN AIRPORTS **(See RADIOIODINE TREATMENT)**

RADIOIODINE TREATMENT

You May Set Off The Alarm and be Strip-searched

You Should Avoid Conceiving for A Year

8-13 TRIGGERING RADIATION ALARMS AFTER RADIOIODINE TREATMENT.

WHAT TO TELL PATIENTS ABOUT RADIOIODINE THERAPY

Administration of radio-isotopes makes patients temporarily radioactive. By activating the ever more sensitive airport radiation detectors, false alarms may be triggered. Patients and doctors may not be aware of this risk, and the potential problems it may produce.

This article reports a case of a 46 year old man who was treated with ^{131}I for thyrotoxicosis. Six weeks after the treatment, he set off a detector in an airport. He was immediately detained and strip-searched. A prolonged period of interrogation ensued.

The number of days up to which patients might trigger alarms varies from 95 for ^{131}I, to 3 for Technicium-99m

An accompanying article suggests several precautions for patients receiving radioiodine therapy

---

The primary burden of informing patients and helping them avoid potentially devastating outcomes as well as false alarms rests primarily on the medical personnel administering the isotope. I wonder if informing the airline would ease the path through the gate.

When primary care clinicians refer patients for a procedure involving a radio-isotope procedure they should double-check whether the patient has received adequate forewarning.

RANIBIZUMAB (See MACULAR DEGENERATION)

READING OF MEDICAL AND RELIGIOUS TEXTS

"Most Proponents Of E-BM Adopt A Balanced View."

11-11 ANALOGIES BETWEEN READING OF MEDICAL AND RELIGIOUS TEXTS

Conventional medicine can be seen as a belief system characterized by a profession of faith in evidence-based medicine (**E-BM**). Faith in E-BM follows from the benefits it has delivered in the past, and continues to deliver. It is the best method we have for navigating our way through potential new treatments.

E-BM is analogous to many religious traditions. It is a canon of sacred texts (medical literature). Differences in interpretation can often be traced to different assumptions underlying our reading of the literature.

Just as there are fundamentalist, conservative, and liberal views of religious texts, there are fundamentalist, conservative, and liberal views of E-BM.

The editorialist goes on to describe some analogies between religious fundamentalism and medical fundamentalism.

Most proponents of E-BM adopt a balanced view. They emphasize the limitations of E-BM, the need for judgment in applying it to individual patients, and the validity of evidence other than randomized, controlled trials. They tend to see the literature as a guide, establishing principles that need to be applied to specific situations.

Randomized, controlled trials may show a consistent improved survival for a defined period. “The main difficulty in applying these data is the external validity.” How should we treat the patients with serious co-morbidity? And patients who do not meet inclusion criteria of the trial?

I enjoyed abstracting this commentary. I felt, however, that the editorialist painted the analogy with too broad strokes. Medical fundamentalism is not that “fundamental”. I do not believe that primary care clinicians are strict “medical fundamentalists”. Most will be selective in applying the treatment provided to subjects in a randomized-controlled trial (RCT). They know that their individual patient may vary from patients entered into the trial. Their individual patient may well be an outlier.

Some individuals will gain a more favorable response than the mean response to the intervention. Some will gain less. Some may be at greater risk of developing an adverse outcome if not treated. Some will be at greater risk of harms if treated.

There are also many social and economic reasons why the treatment recommended by the RCT cannot be applied to an individual patient.

Primary care practice is difficult to do well.

Read the full abstract. Read the original article.

RENIN

10-10 ORAL RENIN INHIBITORS

Inhibition of the renin-angiotensin system is an effective way to intervene in the pathogenesis of cardiovascular and renal disorders.

The idea of blocking the *action* of renin on angiotensinogen (thus reducing levels of angiotensin I and angiotensin II) has existed for many years. Active research to produce an effective oral renin inhibitor has been conducted ever since.

This abstract discusses recent efforts to develop clinically effective renin inhibitors.

Read the full abstract.

Renin inhibition as a possible therapeutic measure is a new concept to me. This is not a practical point at this time. I abstracted the article because of its potential application and its general interest. This also gave me the opportunity to review the details of the A-AI-AII-A system. See the following. RTJ

RENIN INHIBITORS (See RENIN)

RESTLESS LEG SYNDROME

Look For Iron Deficiency

9-8 RESTLESS LEG SYNDROME

RLS has a prevalence of 10% to 15% in white adults. It occurs in children and adolescents as well as adults. In over 1/3 of patients symptoms start before age 10. Most are not diagnosed until middle or late adult life. One study has asked whether "growing pains" in children may be a manifestation.

The International Restless Legs Syndrome Study Group suggests 4 criteria for diagnosis:

1) The desire to move the extremities, often associated with paresthesias or dysesthesias

2) Motor restlessness

3) Aggravation of symptoms by rest, and at least temporary relief by activity

4) Worsening of symptoms in the evening or night.

Iron deficiency is present in about ¼ of patients, particularly in older people. The severity of symptoms is proportional to the reduction in iron. Symptoms severity increases as serum ferritin levels become lower. Reduction of iron in parts of the CNS (shown by MRI) and reduced ferritin in the cerebrospinal fluid suggest that iron deficiency may have a role in pathophysiology. The possibility of iron deficiency needs to be investigated and treated. Treatment may reduce symptoms.

Ropinirole (a dopamine agonist often prescribed for Parkinson's disease and for bipolar disorder) is approved for use in RLS in the USA. . It has significant adverse effects, particularly somnolence. It interacts with a number of other drugs.

Both clinician and patients should be aware of all adverse effects. I would not prescribe it for RLS unless the patient has very troublesome symptoms and insists on trying drug therapy.

ROSIGLITAZONE (See DIABETES)

SHINGLES

A Major Boon for the Elderly

7-2 FDA APPROVES SHINGLES VACCINE

On May 26, 2006; the FDA approved the vaccine (Oka/Merck; *Zostavax*). It is indicated for persons age 60 and over who are not immunocompromised, (about 44 million) and who have not had a history of shingles.

A major study reported the vaccine reduced incidence of shingles of 51%; reduced severity of the disease by 61%, and decreased incidence of post-herpetic neuralgia of 67%.

The company said the vaccine is available now, priced at about $150. Who will pay? If the CDC advisory Committee on Immunization Practices votes in October on recommendations for whom the vaccine is appropriate, Medicare coverage may follow. Coverage is not available "at this time".

I will certainly take the vaccine. And advise my wife to take it as well.

SMOKING

Six In One Hundred Taking Varenicline Achieved Continuing Abstinence At One Year

7-5 VARENICLINE, A NICOTINE ACETYLCHOLINE RECEPTOR PARTIAL AGONIST, *VS* SUSTAINED RELEASE BUPROPRION AND PLACEBO FOR SMOKING CESSATION.

Varenicline is a non-nicotine high affinity agonist, and simultaneously a partial antagonist, of the nicotine acetylcholine receptor located in the nucleus accumbens. It may be beneficial for smoking cessation. Varenicline acts by 1) stimulating release of sufficient dopamine to reduce craving and withdrawal symptoms which occur after abrupt cessation of nicotine, while 2) simultaneously acting as a partial antagonist by blocking the binding of nicotine and reducing smoking satisfaction.

This study randomized 1025 smokers to: 1) varenicline 1 mg twice daily, 2) bupropion SR 150 mg twice daily, or 3) placebo. Before randomization, 30% of over 1400 persons screened were excluded because they did not meet inclusion criteria.

Twenty six % of those assigned to varenicline did not complete the 12 week treatment phase; another 18% did not complete the 12 to 52 week phase.

Continuing abstinence at one year:

Varenicline	28% (not statistically different from bupropion)
Bupropion SR	23%
Placebo	14%

Adverse effects included: weight gain, nausea, headache, and insomnia. Four % discontinued due to adverse effects.

The investigators conclude that “Varenicline is an efficacious therapy for smoking cessation.” The hypothesis that a partial nAChR agonist-antagonist would effectively reduce craving and smoking satisfaction was supported.

I calculated the absolute 52-week benefit of varenicline vs placebo. (See the complete abstract) Compared with placebo, an additional 10% of subjects who present to primary care and have no exclusion criteria for varenicline, and remain on varenicline for 52 weeks remain abstinent. Permanent cessation would likely be lower.

I would not underestimate, however, the benefit to society of achieving a one in 10 goal of permanent cessation. The benefit/harm-cost ratio of varenicline cannot be calculated until we have more information on cost and continuing evidence of harms.

We need much more observation: Could varenicline be combined with buproprion or nicotine replacement? Would sequential administration benefit? Could therapy with varenicline be continued for a longer period?

Taking varenicline for 6 months (vs 3 months) led 7 of 100 subjects to remain abstinent at one year

7-6 EFFECT OF MAINTENANCE THERAPY WITH VARENICLINE ON SMOKING CESSATION

The majority of cigarette smokers who achieve abstinence relapse within the first year and require many more attempts before achieving permanent abstinence.

This trial determined whether smokers who remained abstinent after 12 weeks of varenicline therapy would maintain greater continuous abstinence rates at one year if varenicline was continued for another 12 weeks.

	Varenicline given for 6 months	Varenicline given for 3 months
Abstinent at 3 months	100%	100%
Abstinent at 13 weeks	95%	88%

Abstinent at 6 months	70%	50%
Abstinent at 1 year	44%	37%

(Note the increasing relapse rate over the year.)

The benefit of varenicline given for 6 months (vs 3 months) in promoting abstinence at 1 year is 7 out of 100 (7%).

Of 100 patients taking varenicline for 6 months (vs 3 months), 7 more remained abstinent at one year due to the effect of an additional 3 months of varenicline.

Varenicline is at best a modest help. The success rates in primary care would be more modest. Patients in primary care would be less motivated to abstain than the volunteers screened for the trials in academic centers. They would receive less support and encouragement, and would be more likely to withdraw.

The major problem would remain—how to discourage young persons from starting to smoke.

I applaud drug companies and investigators for maintaining interest in smoking cessation. I hope their efforts will continue.

Varenicline has been approved by the FDA. It will be marketed as Chantix by Pfizer. I expect a flurry of advertisements from the company to the general public. I expect many smokers to request this therapy, relying on a pill to solve their addiction. It takes more than a pill. But, even if few achieve permanent abstinence, achieving abstinence for even one patient is a welcome accomplishment. And helping 7 of 100 patients to achieve abstinence is a major accomplishment.

Over Time, Risks Of The Former Smoker Tend To Approach The Risk Of The Never Smoker.

7-13 REVERSAL OF RISK UPON QUITTING SMOKING

In March 2006, 17 scientists from 8 countries met in Lyon, France to assess the evidence on the reversal of health risks after quitting smoking cigarettes. They considered 10 diseases linked to cigarettes.

The group sought evidence to answer 3 questions:

1) Is the risk for disease lower in former smokers than in continuing smokers?

2) What is the time course of the reduction in risk with continued abstinence?

3) Does the risk return to that of never smokers after long periods of abstinence?

The answers:

1) Yes

2) It may take many years.

3) It may or may not, depending on the disease in question. Risks do decline dramatically over 10 to 20 years.

"There are overwhelming health benefits of quitting smoking that accrue with increasing duration of abstinence for most diseases reviewed." Rarely does the risk for disease decline to that of never smokers, but, with longer and variable periods of abstinence, the risk of the former smoker tends to approach the risk of the never smoker.

"Unequivocally, quitting smoking avoids the further increase in death from cancer, cardiovascular disease, and pulmonary disease caused by continuing smoking."

The article did not mention any connection between pack-years and risks. Quitting at a younger age will confer two advantages: 1) Fewer pack-years of smoking will likely be associated with a greater reduction in risks.

2) Individuals will live longer to experience the reduction in risks.

The sooner you quit, the better. It may take 15 to 20 years to lower risk to normal. But it is likely to do so.

STAPHYLOCOCCUS AUREUS INFECTIONS (See METHICILLIN RESISTANT STAPH INFECTIONS)

STATIN DRUGS (See HEART FAILURE)

STEATOHEPATITIS (See NON-ALCOHOLIC STEATOHEPATITIS)

STROKE

"The Reduction In The Risk Of Fatal Stroke Was Consistent With The Treatment Effect, but Not Significant."

8-11 HIGH-DOSE ATORVASTATIN AFTER STROKE OR TRANSIENT ISCHEMIC ATTACK

This randomized trial compared the effect of high dose atorvastatin (*Lipitor*) vs placebo on risk of stroke after a first episode. (Secondary prevention.)

Randomized over 4700 patients (mean age 63) to: 1) Atorvastatin 80 mg daily, or 2) Placebo.

All patients had a stroke or TIA within 6 months of entry. None had known coronary heart disease. Patients with atrial fibrillation were excluded. Median follow-up = 5years.

Stroke over 5 years (primary outcome)	Atorvastatin	Placebo
Non-fatal stroke	10.4 %	11.8 %
Fatal stroke	1.0 %	1.7 %

(NNT to prevent one non-fatal stroke in 5 years = 71; to prevent one fatal stroke = 143)

Overall mortality (number of deaths)	216	211
Number of patients with hemorrhagic stroke	55	33

(*Ie, no reduction on overall mortality; and an increase in hemorrhagic stroke.)*

Elevation of liver enzymes	2.3%	0.5%
Any adverse event resulting in discontinuation of study treatment	17.5%	14.5%

"Our results support the concept that, from the standpoint of statin treatment, stroke or TIA should be considered a coronary heart disease risk equivalent." "The potential risk of recurrent hemorrhage should be considered when one is deciding whether to administer a statin to patients who have had a hemorrhagic stroke."

Conclusion: In patients with a recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin over 5 years slightly reduced overall incidence of stroke and cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke. Mortality was not reduced.

The study was supported by Pfizer. Look for the "spin".

I would not prescribe 80 mg of atorvastatin for secondary prevention of stroke:

Benefits are not, in my opinion, clinically significant.

It is associated with considerable "bother".

Need for more frequent checks of liver enzymes.

More risks (increased hemorrhagic stroke).

More withdrawals.

Lipitor 80 mg daily for 5 years costs $7500.00. (My calculation.)

The "Money Needed to Treat" **(MNT)** *to benefit one patient over 5 years = $7500 X 72 = $540 000, and to prevent one fatal stroke = $1 072 000*

The benefit / harm-cost ratio of high dose atorvastatin to prevent one recurrent stroke over 5 years is very low.

A more clinically rewarding study of atorvastatin for secondary prevention of ischemic stroke would have compared 10 mg with 80 mg, or to compare with a less expensive, low dose of a generic statin.

Note that many patients in the study had risk factors for stroke and coronary disease at baseline: smoking, hypertension, diabetes, overweight. Lipid control is not the only treatment goal. I presume many patients were treated for these risk factors, but the emphasis was on lipid control—taking a pill vs not taking a pill. This is not the way primary care is practiced.

I believe statin therapy is indicated for primary as well as secondary prevention of ischemic (not embolic) stroke. Although the NNT to benefit one patient will be high, I believe lower doses of less expensive statins (eg, generic simvastatin) would likely be associated with prevention of a second episode, and to a lesser extent a primary episode, and be less likely to cause adverse effects and bother.

TAMSULOSIN (See URINARY SYMPTOMS)
THIAZOLIDINEDIONES (See NON-ALCOHOLIC STEATOHEPATITIS)
TOBACCO (See SMOKING)
TOLTERODINE (See URINARY SYMPTOMS)
TRANSIENT ISCHEMIC ATTACK (TIA) (See STROKE)
TYLENOL (See ACETAMINOPHEN)

URINARY STONE

A Greater Likelihood Of Spontaneous Passage.

9-3 MEDICAL THERAPY TO FACILITATE URINARY STONE PASSAGE: A Meta-Analysis

Provided these patients do not require renal pelvic decompression (because of a solitary kidney or obstructing pyelonephritis), and if pain relief can be obtained, a trial of conservative non-surgical therapy may be warranted. Many of these stones pass spontaneously, especially small ones (5 mm and under) located distally in the ureter.

Calcium channel blockers and adrenergic alpha antagonists have been proposed as a way to enhance passage. Use of these drugs is based on our understanding of ureteral smooth-muscle physiology.

This meta-analysis included 9 randomized, controlled trials (over 650 outpatients) in which calcium blockers (eg, nifedipine) or alpha blockers (eg, tamsulosin; *Flomax*) were used. In most patients, the stone was located in the distal third of the ureter.

Control groups were defined as those not having received any additional medical therapy to ease stone passage (eg, no other vasodilators, no antispasmotics or anticholinergic drugs).
Both groups received NSAIDs (eg, diclofenac) for pain control. NSAIDs are highly effective in symptomatic relief of acute renal colic.

Overall, patients given a calcium blocker or an alpha blocker had a 65% greater likelihood of stone-passage than controls. The calculated number needed to treat (NNT) to obtain one
passage = 4.

"With the low risk-profile of these drugs, and their wide therapeutic window, our results suggest that physicians should consider a new algorithm for the management of urolithiasis in which treatment begins with a course of medical therapy."

The investigators suggest that corticosteroids might provide additional benefits.

Conclusion: Medical therapy is an option for facilitation of urinary-stone passage for patients amenable to conservative management.

Is there any reason why a calcium blocker and an alpha blocker could not be combined? And a corticosteroid added, since treatment period is short?

URINARY SYMPTOMS

11-10 TOLTERODINE AND TAMSULOSIN FOR TREATMENT OF MEN WITH LOWER URINARY TRACT SYMPTOMS AND OVERACTIVE BLADDER

Overactive bladder syndrome (**OABS**) is characterized by urinary urgency, and increased frequency during the day and night—with or without incontinence. An estimated 10 million men over age 40 have symptoms consistent with OABS. The symptoms are often attributed to detrusor overactivity, characterized by involuntary detrusor contractions during bladder filling. Detrusor overactivity may co-exist with bladder outlet obstruction due to benign prostatic hyperplasia (**BPH**)[1].

The resultant increased pressure leads to structural changes in the bladder, which in turn increases the excitability of detrusor smooth muscle. Outlet obstruction may cause urinary hesitancy, intermittency, weak stream, and other lower urinary symptoms.

This randomized, double-blind, placebo-controlled trial followed 879 men (mean age 62). All had documented symptoms of overactive bladder with 8 or more micturations daily, and urgency symptoms 3 or more times daily, with or without incontinence.

Randomized to: 1) tolterodine ER (*Detrol ER* 4 mg daily; blocks the muscarine receptor of acetylcholine;) 2) tamsulosin (*Flomax* 0.4 mg daily; blocks adrenergic action on the prostate smooth muscle), 3) both together, or 4) placebo. Follow-up for 12 weeks:

Placebo Tolterodine ER Tamsulosin Both

Treatment benefit	(%)	62	65	71	80

(In absolute terms, the difference between placebo and two drugs combined was 18%; NNT to benefit one patient = 6.)

Conclusion: Treatment with combined tolterodine ER + tamsulosin resulted in clinically significant benefit for men with moderate to severe lower urinary tract symptoms.

Primary care clinicians might choose to prescribe one drug to test its benefit, and add the second drug if response is not satisfactory.

VACCINATION (See INFLUENZA)

VACCINES (See INFLUENZA)

VALVULAR HEART DISEASE

"More Than One In Eight People Aged 75 and Older Have A Moderate Or Severe Valve Disease."

9-11 BURDEN OF VALVULAR HEART DISEASE

Since the incidence of rheumatic fever has fallen dramatically in developed countries, valvular heart disease (**VHD**) is not usually regarded as a major problem. VHD is now mostly degenerative. It is related to the increasing age of the population. Availability of echocardiography has led to an increase in diagnosis.

This study reassessed the prevalence of VHD in the population and its effect on overall survival.

"The population burden of clinically noteworthy valvular heart disease is considerable in the US population." Prevalence increased markedly with age—from 0.7% in the young group; to 13.3% in the 75 and older group. Prevalence begins to increase at age 65. "More than one in eight people aged 75 and older have a moderate or severe valve disease." The estimate of prevalence of VHD in the USA corresponds to a burden in the year 2000 of 4 to 5 million adults.

VHD is not benign. Over 10 years after diagnosis, mortality rates were increased in those with VHD—adjusted risk ratio = 1.36 (valve disease vs no valve disease). Risk of death increased each year.

Conclusion: Moderate or severe VHD is common in the population. It increases markedly with age, and is associated with increased mortality.

This begs the question—What should primary care clinicians do with a patient with VHD? The response depends on many factors (age, type of VHD, co- morbidity, preferences of the patient, availability of expert surgeons)—not an easy decision to make.

Another problem: Does VHD predispose to endocarditis secondary to bacteremia associated with dental manipulations? This has been debated. The increasing prevalence of VHD in the elderly renews the debate. Should patients with VHD receive antibiotic prophylaxis when undergoing invasive dentistry?

VARENICLINE (See SMOKING)

VENOUS THROMBOSIS

As Effective and As Safe As LMWH. Suitable for Outpatient Treatment.

8-9 COMPARISON OF FIXED-DOSE WEIGHT-ADJUSTED UNFRACTIONATED HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN FOR ACUTE TREATMENT OF VENOUS THROMBOSIS.

This trial was designed to determine if fixed-dose weight-adjusted unfractionated heparin given s.c is as effective and safe as LMWH in treatment of VTE.

Randomized, non-inferiority trial followed over 700 patients (mean age 60) with acute VTE. All had newly diagnosed VTE confirmed by venography or ultrasonography, or pulmonary embolism confirmed by CT angiography.

Randomized to:

1) Unfractionated heparin given s.c.—initial dose = 333 U/kg; followed by 250 U/kg every 12 hours.

2) LMWH (dalteparin or enoxaparin) given s.c at a dose of 100 IU/kg every 12 hours.

No coagulation tests were used to modify doses.

Both drugs were administered for at least 5 days. Both were overlapped with warfarin, usually started on the first day as heparin, and continued for at least 5 days. Most subjects were treated as outpatients.

Recurrent VTE	Unfractionated heparin (n = 345)	LMWH (n = 352)
Three months	13 patients (3.8%)	12 patients (3.4%)
DVT recurrence	11 patients	8 patients
PE	2 patients	4 patients.
Deaths 3 months	5.2%	6.3%
Major bleeding (1st 10 days)	4 patients (1.1%)	5 patients (1.4%)

Conclusion: Fixed-dose subcutaneous heparin is as effective and as safe as LMWH of initial treatment of venous thromboembolism. It is suitable for treatment of outpatients. It is much less expensive.

A disadvantage of unfractionated heparin is that it is more likely to cause heparin-induced thrombocytopenia (with sometimes devastating thrombotic complications) than is LMWH. However, it occurs rarely.

The benefit/harm-cost ratio of s.c. unfractionated heparin is much higher than the ratio for LMWH because the cost is so low in comparison.

WAIST CIRCUMFERENCE (See OBESITY)