PRACTICAL POINTERS

FOR

PRIMARY CARE MEDICINE

INDEX

JULY - DECEMBER 2009

PRACTICAL CLINICAL POINTS

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO FULL ABSTRACTS

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

The numbers in the brackets refer to the abstract. For example, [7-6] refers to the sixth article abstracted in July .

It consists of 4 parts:

1) "Practical Clinical Points": This provides an instant reminder of points of clinical interest and importance which primary care clinicians may wish to advise patients about, consider, and be aware of. Some points are new; some emphasize older points.
2) "Medical Subject Headings" (MeSH): A list of 52 medical subject headings from Alzheimer's disease to Vitamin D, arranged alphabetically.
3) "Highlights of Abstracts and *Editorial Comments*" section: linked alphabetically to each MeSH. (There may be several articles listed under a MeSH.) The highlights contain a condensation of each abstract. The *Editorial Comments* are those of the editor alone, based on his years-long experience as a practicing primary care internist and as editor and publisher of *Practical Pointers for Primary Care Medicine*
4) The abstract itself may be accessed from the monthly issues on the website, which provide more detailed information, and the citation.

Monthly issues for the past 10 years may be found on the website (www.practicalpointers.org).

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

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

PRACTICAL CLINICAL POINTS JULY - DECEMBER 2009

Physical activity and diet are independently associated with reduced risk of Alzheimer disease.[8-4]

Authors are still considering the "Polypill " principle in primary prevention of cardiovascular disease--combining, in one pill, several established low-cost, low-adverse effect drugs to be given to a high risk population without pretesting and without follow-up. [11-5]

For carpel tunnel syndrome surgery (vs splinting) results in more rapid symptom improvement, and more complete recovery. Patient preference is important. [9-6]

More frequent application of screening spirometry may detect COPD at an earlier stage and improve outcomes [8-2]

High-flow oxygen is an effective and safe treatment for cluster headache [12-3]

Community-acquired pneumonia treatment should cover both typical and atypical organisms [9-1]

Current evidence is insufficient to assess the balance of benefits and harms of using non-traditional risk factors to screen for asymptomatic coronary heart disease. [8-7]

C-reactive protein is independently associated with incident coronary heart disease. The clinical implications of this finding are not clear [10-4]

Dabigatran, a new direct thrombin inhibitor is non-inferior to warfarin in prevention of thromboembolism secondary to atrial fibrillation. It is much easier to apply: twice daily oral dose; no monitoring of the effect. Risks of hemorrhage are comparable to warfarin. [9-4]

Advanced dementia is a terminal illness [10-7]

Angiotensin II blockers and ACE inhibitors do not protect the kidney from adverse effects of type 1 diabetes. They may reduce risk of retinopathy [7-8]

Tight control of systolic BP to less than 130 decreases the likelihood of left ventricular hypertrophy. [8-5]

A Mediterranean style diet delays the need for anti-hyperglycemic drug therapy for newly diagnosed type 2 diabetes and leads to more factorable glucose control and coronary risk factors.]9-3]

Patient with diabetes are more likely to receive antidiabetes medication, which has not been shown to reduce CVD risk, rather than antihypertensive medications and statins. [10-2]

The potential for preventing morbidity and mortality through healthy living is enormous [8-1]

Maintenance of healthy lifestyles is critical to lowering risk of heart failure [7-1]

Dietary supplements are an emerging risk to public health. Many products contain undeclared active pharmaceutical agents. Many are contaminated with toxic plant materials, heavy metals, and bacteria. An estimated 15% of U.S. adults use them for weight loss [10-1]

Intravenous iron is a potential new avenue for treatment of heart failures [12-7]

Modest increases in HDL-cholesterol are associated with a reduction in risk of cardiovascular disease [10-5]

Rates of hip fracture in the U.S. elderly have declined, possibly due to widespread use of bisphosphonates [10-8]

Should the human papilloma virus vaccine be given to boys and men? [7-7]

The adjuvated human papilloma virus vaccine provides protection for at least 6 years [12-2]

Diet and lifestyle factors have the potential to prevent a large proportion of new-onset hypertension in women [7-1]

Fifty years on, thiazides maintain a prominent role in treatment of hypertension [11-4]

Lipid measurements can be simplified by measurement of total cholesterol and HDL-cholesterol without the need to fast or to measure triglycerides. [11-3]

Effects of mammography screening under different screening schedules--the basis for the new USPSTF recommendations of screening. [11-1]

The USPSTF recommendations for mammography screening [11-2]

Close adherence to the traditional Mediterranean diet is associated with lower overall mortality. [7-4]

Migraine with aura, especially in younger women who smoke and take oral contraception, increases risk of ischemic stroke [12-5]

Liraglutide, a glycogen-like peptide now used to treat diabetes, may offer a new mode of action to treat obesity [11-6]

Seven symptoms associated with ovarian cancer. Ovarian cancer can no longer be regarded as a "silent killer" [9-5]

New American Geriatric Society guidelines for pain control in the elderly--avoid NSAIDs, use opioids. [7-5]

Famotidine, a histamine blocker, is effective for prevention of gastric ulcer in patients taking low-dose aspirin [7-6]

Lemierre syndrome, due to *Fusobacterium necrophorum***, associated with pharyngitis in young adults, requires special recognition and treatment. It can be deadly [12-8]**

Initiating physical activity, as well as continuing physical activity is associated with better survival and function in the elderly. [9-2]

The current pattern of medical imaging is exposing many patients to substantial doses of radiation [8-8]

Salt has been a clinically neglected risk factor for hypertension, Aim for no more than 5 grams daily [12-1]

Repeated cycles (up to 4) of pharmacotherapy for smoking cessation may lead to permanent abstinence [11-7]

Combined bupropion + nicotine lozenge may be more effective in achieving abstinence from cigarettes than either drug alone [12-6]

A single dose of corticosteroids, may lessen pain of severe sore throat [8-3]

Statin drugs reduce risk of all cause mortality in individuals who have no established risk factors for CVD [7-3]

Sensitive troponin assays, combined with clinical data, are a step forward in diagnosis of myocardial infarction [8-6]

The D-Dimer test can rule out venous thromboembolism, not rule it in [8-6]

Vitamin D reduces risk of falling [10-6]

Low vitamin D levels are associated to poor health outcomes from a variety of health conditions in a large proportion of the U.S. population [12-4]

MEDICAL SUBJECT HEADINGS (MeSH) JULY - DECEMBER 2009

ALZHEIMER DISEASE
ASPIRIN
ATRIAL FIBRILLATION

BREAST CANCER

CARDIOVASCULAR DISEASE
CARPAL TUNNEL SYNDROME
CHRONIC OBSTRUCTIVE PULMONARY DISEASE
CLUSTER HEADACHE
COMMUNITY-ACQUIRED PNEUMONIA
CORONARY HEART DISEASE
C-REACTIVE PROTEIN

DABIGATRAN
DEMENTIA
DIABETES
DIET
DIETARY SUPPLEMENTS
D-DIMER TEST

FALL PREVENTION

HEALTHY LIVING:
HEADACHE
HEART FAILURE
HDL CHOLESTEROL
HIP FRACTURE
HISTAMINE BLOCKER
H1N1 FLU
HUMAN PAPILLOMA VIRUS
HYPERTENSION

LEMIERRE SYNDROME
LIFESTYLE FACTORS
LIPIDS

MAMMOGRAPHY
MEDICAL IMAGING
MEDITERRANEAN DIET
MIGRAINE

OBESITY
OVARIAN CANCER

PAIN
PEPTIC ULCER
PHARYNGITIS
PHYSICAL ACTIVITY
PNEUMONIA

RADIATION
RENIN-ANGIOTENSIN SYSTEM

SALT
SLEEP
SMOKING
SORE THROAT
STATIN DRUGS
STROKE

TROPONIN ASSAYS

VENOUS THROMBOEMBOLISM
VITAMIN D

ALZHEIMER DISEASE

Independently Associated With Reduced Risk Of AD.

8-4 PHYSICAL ACTIVITY, DIET, AND RISK OF ALZHEIMER DISEASE

The effect of combined Mediterranean diet (**MD**) + physical activity (**PA**) on Alzheimer disease (**AD**) has not been studied. This study examined the effect of the association. It included two cohorts (n = 1880; mean age 77) recruited through a neighborhood aging project 1992-99.

Neuropsychological status: None had dementia at baseline. At entry, recorded each individual's medical and neurological history. A neuropsychological battery tested memory, orientation, abstract reasoning, language, comprehension, and visual-spatial abilities. Repeated evaluations every 1.5 years through 2006. Made a consensus diagnosis for presence or absence of dementia.

Physical activity: Assessed PA by a leisure-time questionnaire—the number of times and the number of minutes participating in 3 categories: vigorous, moderate, and light.

A summary physical activity score was categorized into tertiles.

a. None: 0 hours.

b. Some: 0.1 hours of vigorous and 0.8 hours of moderate, or 2.3 hours of moderate or light, or a combination thereof.

c. High: 1.3 hours of vigorous, 2.3 hours of moderate or 3.8 hours of light, or a combination thereof.

Diet: Obtained average food consumption information over the past year with a food intake questionnaire. Constructed a MD diet score. Assigned a value of 1 for each *beneficial* component: fruits, vegetables, legumes, cereals, fish, a ratio of monounsaturated fat to saturated fat, and mild to moderate alcohol consumption *above* the median. Also assigned a value of 1 for each *detrimental* component (meat and dairy) *below* the median.

Analyzed into tertiles: low 0 to 3; middle 4 to 5; high 6 to 9.

Individuals were then classified into 4 groups:

Low PA + low diet score

Low PA + high diet score

High PA + low diet score

High PA + high diet score.

A total of 282 incident cases of AD occurred during a mean of 5 years.

Hazard ratios (**HR**) of AD:

High MD adherence (HR compared with low adherence) = 0.60

High physical activity (HR compared with no physical activity) = 0.67

Hazard ratios for AD incidence by PA and diet scores:

Low PA + low diet score	1.00 (reference)
Low PA + high diet score	0.77
High PA + low diet score	0.81
High PA + high diet score	0.65

(Adjusted for multiple possible confounders)

Compared with individuals adhering to neither the MD, nor participating in PA, the high diet + high PA individuals had a lower risk of AD. (Absolute risk reduction = 12%; HR = 0.65)

Conclusion: In this study, adherence to both higher MD and higher PA were independently associated with reduced risk of AD. High adherence to both was associated with an absolute reduction in AD of 12%

This is potentially an important advance. Much more work will be required to establish a definite connection. Watch for developments.

We have a way to go before concluding that diet + physical activity influence incidence of AD. Meanwhile, we can continue to advise healthy eating and PA, which are related to decreased incidence of cardiovascular disease, including cerebrovascular disease (vascular dementia). If incidence of AD is also decreased, there is an extra-added attraction.

ASPIRIN (See PEPTIC ULCER [7-6])

ATRIAL FIBRILLATION (See DABIGATRAN [9-4])

BREAST CANCER (See MAMMOGRAPHY)

CARDIOVASCULAR DISEASE (See also STATIN DRUGS [7-3])

Should The Availability Of An Inexpensive, Safe And Effective Preventive Treatment Be Widened?

11-5 PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

In the 1980s, Rose coined the term “prevention paradox” to describe the fact that a large proportion of cardiovascular disease (**CVD**) events occur among the many individuals with average risk factor values. He distinguished between 2 approaches to CVD prevention:

1) The high-risk strategy aims to truncate the upper tail of the normal distribution of risk

factors. It focuses on individuals who are most likely to benefit personally from preventive treatment..

2) The population-based strategy aims to shift the entire risk distribution.

Soon, the high-risk approach came to be synonymous with the use of drugs. (Targeting high-risk individuals with preventive drug therapy benefits the individuals, but does little to reduce the overall burden of CVD on the population.)

The population approach was identified with efforts to shift norms of diet, physical activity, and smoking. Modest lifestyle changes could be recommended to the population at large because sensible interventions such as low-salt diet may be presumed to be safe.

Risk models were then developed to estimate individual risk at the point of care. The models accurately assigned individuals to different risk groups. But they failed to efficiently distinguish or discriminate between individuals who will or will not experience a CVD event.

Two recent developments provide an opportunity for a fresh approach:

1) The cost of the original statins has decreased precipitously.

2) The efficacy and safety of statins, especially at low to moderate doses, is established.

The widely accepted threshold of a 10-year CVD risk of 20% means that a large proportion of men 50 years and older is already eligible for statins. As a result, long-term mass preventive therapy would occur de facto in this group.

“Because 96% of all CVD events occur in persons older than 55 years, and because risk equations are poor at discriminating events, an alternative proposal is simply to offer generic statins, perhaps as part of a combination-drug polypill to all adults on the basis of age threshold regardless of the level of LDL-cholesterol, CRP, or absolute risk.”

Preparations containing a statin and effective and safe BP-lowering agents such as low-dose diuretics are already being evaluated for wider use. An age-based approach obviates the need for a resource-intensive check for CVD risk, and would extend preventive drug therapies to individuals at lower individual risk.

Lifestyle interventions are generally ineffective.

The “polypill” concept refuses to die. Applying a preventive intervention to the general population is already an accepted application in the U.S. (Eg, the administration of vaccines.)

Traditional Western medicine relies on 1) testing for risk, 2) prescribing for individual patients with risk above a defined, but arbitrary level, 3) monitoring for adverse effects and effectiveness of response

by retesting. Should the response be less than predicted by the arbitrary level, the dose of the drug is increased.

The polypill concept relies on evidence that, at any BP or LDL-c level, reducing that level will result in a constant relative risk reduction, but with an ever-diminishing absolute risk reduction.

Clinicians can often tell at a glance, without testing, individuals who are at increased risk of CVD. (Mall watching will reveal how high the risk of CVD is in the general population.)

Simply checking the BP will augment reliability of the predication.

I would judge that acceptability of a pill would be greater than a life-style change. People find it easier to take a pill. But, would the population comply with taking a daily pill for years without any obvious benefit?

Primary care clinicians may consider it risky to prescribe without pre-testing and follow-up.

Would there be legal risks?

I believe the benefit / harm-cost ratio of a polypill would be very high, especially in some populations.

CARPAL TUNNEL SYNDROME

Between Two Levels Of Severity, Decision Is More Difficult. Patient Preference Is Important

9-6 NON-SURGICAL TREATMENT IN CARPAL TUNNEL SYNDROME

It is generally accepted that severe CTS, manifested by thenar eminence atrophy and severe sensory loss requires surgery. Surgeons do not usually encourage surgery in patients with mild symptoms, no functional limitation, or no neurological deficit.

Between these two levels of severity, the decision is more difficult.

A multicenter randomized trial entered 116 patients with idiopathic CTS, normal two point discrimination, and no thenar atrophy. Most had abnormal median nerve conduction tests and moderately severe disease.

Non-surgical treatment: Mainly hand exercises (ligament stretching and tendon gliding exercises) and wrist splinting. (Wrist splinting is the most common non-surgical treatment.) Most non-surgical patients received, to varying degrees, several of the non-invasive treatments available. Treatments were intensive, requiring repeated hand therapy. Non-improvers were offered ultrasound. (Hand-wrist exercises and ultrasound did not provide additional benefit beyond that offered by splinting alone.) There was a substantial non-adherence to those treatments. There was a large cross-over to surgery. Patients who do not have satisfactory improvement with non-surgical treatment should be offered surgery.

Surgery: Abundant evidence from randomized trials supports the high effectiveness of surgery (open or endoscopic tunnel release). Patient-reported measurements of functional status and symptom severity showed that surgery was significantly more efficacious than non-surgery at 6 and 12 months. The differences were modest (0.4 on 1-5 scale) on an intention-to-treat basis. Of the patients who actually underwent surgery, 88% had symptom improvement. Surgery results in rapid symptom relief. Non-surgery does not. At 6 months and at 12 months, surgery patients had less pain. And surgery, more often than splinting, results in complete recovery as opposed to improvement.

Patient preference is important. Faced with the need to wear a splint every night and during the daytime for weeks some might prefer surgery; others may prefer partial recovery to potential surgical risks.

The authors tilt toward surgery. I would not tarry too long with non-surgical treatments.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

"The Spirometer Is To COPD What The Sphygmomanometer Is To Hypertension."

8-2 SCREENING FOR AND EARLY DETECTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

This review of COPD was based on an extensive literature search. It summarizes new developments and diagnostic techniques and provides an updated account of controversies and research needs with respect to screening.

Prevalence: COPD is a leading cause of death. Overall, the prevalence of COPD in the general population is an estimated 8-10% of individuals over age 40.

Prevention: An important part of primary care relates to secondary prevention—early detection of disease and monitoring for chronic illness. "We have a professional duty to diagnose early, and monitor various disorders without actively treating them, except with lifestyle advice".

Screening and Diagnosis: Spirometry is an important method for accurate diagnosis and effective management of COPD. It is simple, reliable, safe, and non-invasive. It is essential for diagnosis of COPD. The American College of Physicians and the USPSTF recommend that screening spirometry should *not* be preformed on asymptomatic persons. Although not proven, intervention at a very early stage might reduce the likelihood of developing future COPD. Early diagnosis can be compared with screening programs for hypertension and hyperlipidemia.

Spirometry in primary care: "The spirometer is to COPD what the sphygmomanometer is to hypertension." Primary care is an essential focal point for any antismoking intervention. All guidelines

(except NICE) require post-bronchodilator spirometry values. However, FEV1 and other respiratory indices obtained without bronchodilation are good markers.

Handheld spirometers have been developed and improved, with user-friendliness that makes them acceptable for use in general practice. Difficulties with validation remain. A relaxation of the stringent ATS/ERS spirometry criteria might make spirometry more accessible to primary care for case exclusion at the point of consultation and boost the rate of detection.

Prognosis: Undetected disease could go on to cause substantial morbidity and mortality.
The prospective Lung Health Study followed 6000 subjects with mild-moderate COPD (mean 78% of predicted FEV1). Subjects were offered a smoking-cessation program. About 25% stopped smoking completely and another 25% stopped to the end of the study. Those who stopped smoking showed a small improvement in lung function over the first year, and had reduced rates of decline thereafter. At an 11-year follow-up, almost all smokers who were abstinent at 5 years remained abstinent. Those who continued to smoke lost, on average, 30 mL of expiratory volume per year more than quitters. Those who stopped reported improved symptoms of cough, phlegm, and wheeze.

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http://ajrccm.atsjournals.org/cgi/content/full/159/1/179

This is the view from Spain. Our colleagues in Barcelona have had extensive experience with COPD. Regardless of the opinion to the USPSTF, these authors encourage screening in primary care. Spirometry can be complex and expensive. It can be inexpensive and simple, especially if bronchodilation is not used. There is no reason why basic screening spirometry should not be used in primary care, especially in smokers. Early detection of a decrease in FEV1 and the ratio of FEV1/FVC might encourage some smokers to quit.

If we use spirometry to follow patients with asthma, why not COPD?

CLUSTER HEADACHE

"Cluster Headache Is Probably The Most Severe Pain Known To Humans."

12-3 HIGH-FLOW OXYGEN FOR TREATMENT OF CLUSTER HEADACHE

Cluster headache (**CH**) is a stereotypic primary headache syndrome characterized by attacks of unilateral excruciating pain, usually in the eye, periorbital region, and temple, with associated cranial autonomic symptoms such as conjunctival injection, lacrimation, nasal blockage, rhinorrhea, ptosis, and eyelid edema. During attacks, patients are often restless and agitated,

Untreated, attacks usually last for 15-180 minutes and have a frequency of 1 every other day to up to 8 attacks per day.

Attacks usually occur in bouts or clusters lasting for weeks or months, separated by remissions lasting months or years.

Treatment relies on therapy to abort the individual attack, and prophylactic therapy to prevent or suppress attacks when they occur. Therapy for attacks must be fast-acting.

Serotonin receptor agonists (sumatriptan; zolmitriptan) are the most effective treatment for acute CH.

Drawbacks for triptans include limitations of daily usage in order to prevent tachyphylaxis and rebound. Triptans are contraindicated in patients with cardiovascular disease.

This randomized, placebo-controlled, double-blind crossover study (2002-2007) compared;

1) 100% oxygen at 12 L/min delivered by a facemask for 15 minutes from the beginning of an attack, or

2) Air delivered the same way.

At end point:	O2	AIR
No of attacks treated	150	148
Pain free at 15 min	78%	20%

(By my calculation, the NNT with oxygen to render one patient pain-free at 15 minutes = 2 RTJ)

Reduction of pain (%)		
15 min	68	20
20 min	81	30
30 min	85	38
60 min	92	59
Need for rescue meds within 15 min (%)	28	53

At all time points, oxygen was superior to air in reducing secondary endpoints.

CONCLUSION

Treatment of patients with CH at symptom onset using inhaled high-flow oxygen compared with placebo was more likely to result in being pain-free at 15 minutes.

CH have been termed "suicide headache".

If you practice primary care medicine long enough, you will encounter a patient with CH. These patients are desperate. Any patient who gains relief of pain will be most grateful.

Oxygen therapy might be inconvenient, but may be made available most of the time.

Triptans increase BP, and are contraindicated in many patients.

Which therapeutic modality to use (or both) would be a matter of trial and error in the individual.

The article did not deal with prophylactic therapy.

COMMUNITY-ACQUIRED PNEUMONIA

Cover Both Typical And Atypical Organisms

9-1 GUIDELINE-RECOMMENDED ANTIBIOTICS IN COMMUNITY-ACQUIRED PNEUMONIA: Not Perfect, but Good

Patients hospitalized with community-acquired pneumonia (**CAP**) can be infected with both typical and atypical (eg, *Legionella*) bacteria. Clinical features at presentation are not specific enough to consistently predict the causative agent. Absent unique epidemiological characteristics, the overwhelming majority of patients must be treated empirically.

Guidelines have been published recommending specific empirical antibiotic regimens. (*See the full abstract*)

A growing body of evidence supports the use of empirical regimens to target both typical and atypical organisms.

Three retrospective cohort studies in different settings reported that patients who received guideline-concordant antibiotics had decreased in-hospital and 30-day mortality. Two large Medicare studies of elderly patients admitted with CAP also reported a lower 30-day mortality in patient treated with antibiotics compliant with guidelines. After attempts were made to control for potential confounders, benefits were significant. The absolute risk reduction averaged 5%. (NNT = 20).

Two articles in this issue of *Archives* add to the literature regarding appropriate empirical use of antibiotics for CAP. They support the current guidelines. (*See the full abstract*)

For clinicians, the 2 studies add to the growing body of robust evidence supporting guideline-recommended antibiotic regimens. No research has documented clear negative consequences to these regimens. Adverse effects remain hypothetical in the face of potentially substantial mortality benefit.

"While we await further research, patients hospitalized with CAP should receive treatment with guideline-concordant antibiotic regimens covering both typical and atypical organisms."

I recall, years ago, a patient who died in the hospital with CAP. She was a relatively young women and a good personal friend of mine. We struggled mightily to save her. Such patients are unforgettable.

I believe if we had the appropriate antibiotics and the present knowledge, we could have saved her.

The benefit / harm-cost ratio of combined antibiotics in severely ill patients with CAP is very high. I would not let putative adverse effects deter me.

CORONARY HEART DISEASE **(Also see TROPONIN [8-7])**

Evidence is Insufficient To Assess The Balance Of Benefits And Harms Of Using Nontraditional Risk Factors

10-3 USING NON-TRADITIONAL RISK FACTORS IN CORONARY HEART DISEASE RISK ASSESSMENT: *U.S. Preventive Services Task Force Recommendation Statement*

Since 1996, reviews were conducted on 9 proposed nontraditional risk factors:

High sensitivity C-reactive protein (**hsCRP**)

Ankle-brachial index (**ABI**)

Coronary artery calcification score on electron-beam commuted tomography (**CAC**)

Leukocyte count

Fasting blood glucose

Periodontal disease

Carotid intima-media thickness

Homocysteine

Lipoprotein (a)

The reviews followed a hierarchical approach aimed at determining which factors could practically and definitively reassign persons who are assessed as intermediate-risk (10% to 20% risk of myocardial infarction and coronary death over the next 10 years according to the Framingham score) to either a high-risk strata, or a low-risk strata. In those reassigned to a high-risk strata, outcomes may be improved by aggressive risk-factor modification. (In the US, about 30% of asymptomatic men and 7% of asymptomatic women fall into the intermediate-risk category.)

“Clinicians should continue to use the Framingham model to assess CHD risk and guide risk-based preventive therapy.”

“The USPTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of using the nontraditional risk factors discussed in this statement to screen asymptomatic men and women with no history of coronary heart disease to prevent CHD events.”

Clinicians should understand the evidence. And individualize decision making in the specific patient.

This does not say that non-traditional risk factors are valueless. It says merely that we don’t know.

I expect studies to continue assessing these and other putative risk factors. Note that body mass index, which is a valid risk factor, is not included in the Framingham score.

The study was restrictive. It concerned only those risk factors that might re-classify Framingham risk from intermediate (10-20% risk in the next 10 years) to high (over 20%).

Is the Framingham risk score useful in primary care medicine?

I believe it is not very useful. The score attempts to identify patients who have a 10% to 20% risk of MI or cardiac death over the next 10 years. Primary care clinicians look far beyond 10 years.

Younger persons with a serious risk factor (eg, smoking or high LDL-cholesterol) and no other risk factors may have a low score. Certainly, this should not preclude preventive treatment.

All established risk factors should be treated individually even though the calculated risk is low.

C-REACTIVE PROTEIN

"CRP Levels Are Independently Associated With Incident CHD." The Clinical Implications Of The Association Of CRP With CHD Events Are Less Clear.

10-4 C-REACTIVE PROTEIN AS A RISK FACTOR FOR CORONARY HEART DISEASE:

Several lines of evidence have implicated chronic inflammation in CHD. Inflammatory markers have received much attention as new or emerging risk factors that could account for some of the unexplained variability in CHD risk.

C-reactive protein (**CRP**) is a sensitive, non-specific systemic marker of inflammation. It is not known, however, if it is involved in pathogenesis of CHD. Elevated levels are associated with traditional risk factors and obesity.

This systematic review and meta-analysis of epidemiologic studies was conducted to help the USPSTF determine whether CRP should be incorporated into guidelines for risk assessment

Risk ratio for CHD associated with CRP levels > 3.0 vs < 1.0:

Pooled RR of eleven good-quality studies combined = 1.58

Risk ratio for CHD associated with CRP 1.0 to 3.0 vs < 1.0:

Pooled RR of twelve good quality studies combined = 1.22

"The body of evidence that CRP level is independently associated with incident CHD is strong."

Little evidence links changes in CRP to primary prevention of CHD events.

The clinical implications of the association of CRP with CHD events are less clear.

"The viability of CHD as a new factor in global risk assessment of incident CHD is limited by sparse evidence that directly links therapeutic changes in CRP level to primary prevention of CHD events."

"Current guidelines recommend aggressive therapy only for high-risk patients, such as those with a Framingham score greater than 20%, diabetes, or known cardiovascular disease."

The implications of the use of CRP in global risk assessment are not clear. The findings have been interpreted to mean that CRP level may represent a different aspect of risk, with complex interrelationships among CRP levels, traditional risk factors, and CHD. Others have concluded that CRP level is largely attributable to traditional risk factors, and CRP may have limited clinical utility.

Conclusion: CRP is independently associated with incident CHD. The clinical implication of this finding is not clear. The pooled risk ratios do not necessarily measure the usefulness of CRP in reclassifying intermediate risk persons. Evidence linking changes in CRP level to primary prevention of CHD is insufficient.

Do we need another risk factor for CHD?

I believe not. We have failed miserably to apply those we have, which we know are valid risk markers. Let us concentrate on those. This does not mean we should quit looking for new risk factors. Premature wide-spread use of a newly described risk factor test, the clinical value of which is dubious, will increase costs of our national health services.

Is high sensitivity CRP a good risk factor?

I believe not. It fails to meet guidelines for a screening test in several respects:

There is no evidence that reducing CRP per se will reduce complications of CHD.

No evidence that a CRP screening program will lead to a reduction in morbidity or mortality from CHD.

CRP has not been adequately evaluated. A suitable cut-off value is not defined and agreed.

The benefit / harm-cost ratio of CRP screening has not been established.

It risks causing harm by overdetection and adverse psychosocial effects.

Will primary care clinicians use CRP for screening?

I believe some will. The lure of the "cutting edge" is strong.

DABIGATRAN

Non-Inferior Obvious Advantages More Expensive

9-4 DABIGATRAN versus WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

Dabigatran etexilate is an oral pro-drug that is rapidly converted in serum to dabigatran, a potent direct competitor of thrombin. Serum half-life is 12 to 17 hours. The drug does not require regular monitoring.

Multi-country trial enrolled (2005-2007) over 18 000 participants (mean age = 71) who had AF and an increased risk of stroke.

Randomized to: 1) dabigatran 110 or 150 mg twice daily orally, or 2) adjusted-dose warfarin to a target INR of 2.0 to 3.0. Concomitant use of aspirin (< 100 mg daily) or other anticoagulant agents was permitted.

The primary analysis was whether either dose of dabigatran was inferior to warfarin. Median duration of follow-up = 2 years.

Primary outcomes (% per year)	Dabigatran (150 mg)	Warfarin
Stroke or systemic embolism	1.1	1.7
Hemorrhagic stroke	0.10	0.38
Death from any cause	3.64	4.13
Myocardial infarction	0.74	0.53
Pulmonary embolism	0.15	0.09
Adverse effects (% per year)		
Major bleeding	3.1	3.4
GI bleeding	1.5	1.02
Minor bleeding	14.8	16.4
Intracranial bleeding	0.30	0.74
Discontinuation (at 2 years)	21	17

The investigators considered the net clinical benefit to favor dabigatran.

Conclusion: In patients with AF, dabigatran was associated with rates of stroke similar to those of warfarin. Rates of hemorrhage were similar. Dabigatran was considered non-inferior to warfarin

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Dabigatran (Pradaxa) is approved in Europe and Canada. It is expensive. The dose is not settled.

This drug has many advantages. It could be used for many indications in which there is an increased likelihood of thromboembolism.

Will thrombin inhibitors supplant warfarin?

As a rule, I do not abstract articles about drugs until the drug is approved by the FDA, and is on the market in the USA. Dabigatran is so potentially important, I decided to abstract this article.

DEMENTIA

"Advanced Dementia Is A Terminal Illness"

10-7 THE CLINICAL COURSE OF ADVANCED DEMENTIA

Dementia is a leading cause of death in the U.S. It is under-recognized as a terminal illness. The lack of information characterizing the final stages of dementia may impede the quality of care provided. Under-recognition of prognosis of advanced dementia may lead to suboptimal palliative care.

This study addressed major gaps in knowledge concerning care for patients with advanced dementia.

Recruited and followed subjects (n = 323; mean age 85; 85% female) between 2003-07 from 22 nursing homes. All patients were age 60 or over and had advanced dementia: inability to recognize family members, minimal verbal communication, total functional dependence, incontinence, and inability to ambulate independently.

Over 18 months, 55% died. The probability death within 6 months was 25%. The probability of pneumonia was 41%; febrile episode 53%; eating problem 86%.

Distressing symptoms included dyspnea (46%), pain (39%), pressure ulcers (39%), agitation (54%), and aspiration (41%). Among those who died, the proportion who had these symptoms increased as the end-of-life approached. In the last 3 months of life 41% underwent at least one burdensome intervention: hospitalization (17%), emergency room visit (10%), parenteral therapy (34%), or tube feeding .

Residents whose proxies had an understanding of the expected poor prognosis and clinical complications were much less likely to receive burdensome interventions than were residents whose proxies did not have this understanding. (Odds ratio = 0.12)

Hospice referral: 22% were referred during the 18 month follow-up period; 26% of these were referred in the final week of life.

Patients with advanced dementia had a 6-month mortality rate of 25% and a median survival of 1.3 years. This is similar to the prognosis for more commonly recognized end-of-life conditions such as metastatic breast cancer and advanced congestive heart failure.

Patients with terminal dementia often receive aggressive treatments such as tube feeding and hospitalization. Aggressive interventions may be needed for pain relief, but this is unusual.

As mortality from many leading causes of death has decreased, deaths from dementia have steadily increased.

Conclusion: Pneumonia, febrile episodes and eating problems are common in patients with advanced dementia, and are associated with high 6-month mortality. Distressing symptoms and

burdensome interventions are common. Patients whose health care proxies understand the prognosis and clinical course are likely to receive less aggressive care at end-of-life.

Communication! Communication! Communication! Primary care clinicians who care for demented patients, especially in nursing homes, have the responsibility of determining the chief proxy of the patient and staying in communication with him or her. Try to avoid the difficulties of multiple proxies.

Advanced directives of the patient must be considered. Try to anticipate and solve any intra-family differences about care. Relatives might be asked: "How would you like to be treated if you were in the same condition?"

We should consider early referral to hospice and palliative care Advanced dementia alone is an adequate reason for referral.

DIABETES

No Benefit From ACE Inhibitor or Angiotensin Blocker

7-8 DIABETES COMPLICATIONS AND THE RENIN-ANGIOTENSIN SYSTEM

The concept has developed that inhibition of the renin-angiotensin system (**R-As**) in patients with diabetes is beneficial in both early and advanced stages of nephropathy.

An extraordinary study in this issue of NEJM challenged the accepted concept. It was the longest study in this field of investigation. It compared strategies for inhibition of the R-As, and evaluated 3 common measures of renal function: microalbuminuria; glomerular filtration rate; and renal morphological features. It also studied the progress of retinopathy.

The findings were surprising. Inhibition of the R-As did not reduce incidence of microalbuminuria, and did not mitigate decline in renal function or renal morphological features. It did reduce progression of retinopathy.

Questions remain.

This study was restricted to a selected group of patients with type-1 diabetes.

I believe the question of benefit or harm on the kidney from R-A blockade is far from settled.

Should primary care clinicians continue to prescribe ACE inhibitors and angiotensin-blockers for patient with diabetes? I would continue because: They are beneficial in treatment of hypertension, which is common in patients with diabetes. They may reduce the complication of retinopathy.

We look for further studies.

Delayed The Need For Drug Therapy And Led To More Favorable Changes In Glycemic Control And Coronary Risk Factors

9-3 EFFECT OF A MEDITERRANEAN –STYLE DIET ON THE NEED FOR ANTI-HYPERGLYCEMIC DRUG THERAPY IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES

Lifestyle intervention studies have demonstrated large reductions in risk for type-2 diabetes (**DM-2**).

The American Diabetes Association (**ADA**) recommends that patient with newly diagnosed DM-2 be treated with pharmacotherapy as well as lifestyle changes. The rationale for combined therapy is that each form of treatment alone is imperfect. Lifestyle changes are often inadequate because patients do not lose weight, or regain weight, or that their diabetes worsens independently of weight.

This randomized trial compared with effectiveness, durability, and safety of a low-carbohydrate Mediterranean diet (**MD**) vs a low-fat ADA diet in patients with newly diagnosed DM-2.

Between 2004-2008 followed 215 overweight patients (mean age 52) with newly diagnosed DM-2. None had been treated with drugs. All were sedentary and had a stable weight over the past 6 months. At baseline, mean BMI = 30. HbA1c = 8%. All received education emphasizing the importance of a healthy diet and physical activity. (**PA**)

Randomized subjects to 1) a low-carbohydrate Mediterranean diet (**MD**), or 2) a low-fat ADA diet.

Mediterranean diet: rich in vegetables and whole grains, and low in red meat. Energy was restricted to 1500 kcal/d in women and 1800 in men, with a goal of a carbohydrate content of less than 50% of daily energy; and less than 30% of calories as fat. (The main source of fat was olive oil.)

ADA diet: Based on ADA guidelines. Rich in whole grains and reduced fat, sweets, and high-fat snacks. No more than 30% of energy from fat, and no more than 10% as saturated fat. Calorie restriction the same as the MD.

After 4 years:	MD	ADA-diet
Requiring drug treatment (%)	44	70 (Almost all with persistent HbA1c >7%)
BMI	- 1.2	-0.9
Waist circumference (cm)	- 3.0	-2.6
HbA1c (%)	-0.9	-0.5

The MD group also had slight advantages in serum insulin, lipids, systolic BP, total energy intake, and carbohydrate and fat intake.

Participants in both groups increased the time spent being physically active, with no statistical significant difference between groups.

Conclusion: Compared with an ADA low-fat diet, a low carbohydrate MD led to more favorable changes in glycemic control and coronary risk factors, and delayed the need for drug therapy in overweight patients with newly diagnosed DM-2.

Another illustration of the importance of lifestyle.

"Patients With Diabetes Are More Likely To Receive Antidiabetes Medication, Which Has Not Been Shown To Reduce CVD Risk, Rather Than Antihypertensive Medications Or Statins."

10-2 TRENDS IN MEDICATION USE AMONG U.S. ADULTS WITH DIABETES MELLITUS: ***Glycemic Control at the Expense of Controlling Cardiovascular Risk Factors***

The impact of tight hyperglycemia control on CVD and mortality risk is not clear.

This study examined the competing treatment priorities for adults with diabetes by analyzing the use of antidiabetes, antihypertension, and statin medications reported by the population-based National Health and Nutrition Examination Survey (NHANES) between 1990 and 2006.

The study was limited to adults over age 20 who reported a history of DM.

Between 1999-2000 and 2005-2006, the use of antidiabetes medications increased, with 90% of US persons with diabetes taking antidiabetes drugs in 2005-2006. The use of these drugs substantially exceeded the proportion of eligible adults with diabetes taking antihypertensives and statins.

The higher rates of use of antidiabetes drugs compared with antihypertensive and statin drugs highlights the concern that a disproportionate emphasis is placed on controlling hyperglycemia at the expense of controlling hypertension and high cholesterol. "Patients with diabetes are more likely to receive antidiabetes medication, which has not been shown to reduce CVD risk, rather than antihypertensive medications or statins."

Control of hyperglycemia frequently takes precedence over control of hypertension and high cholesterol levels among adults with diabetes. This supports the argument for a reprioritization of diabetes treatment goals emphasizing hypertension and lipid control before tight glycemic control as part of an evidence-based CVD risk reduction effort.

Medication use:	1999-2000	2005-2006
Taking antidiabetes drugs	82	90
Taking antihypertensive drugs	68	78
Taking statins	26	51

Glucose control is important. Control is beneficial in preventing micro-vascular disease. It is less important than previously thought for control of macro-vascular disease. I believe that good control does have a beneficial effect on reducing risk of atherosclerotic disease, although it may take years of poor control to cause significant arterial disease.

DIET (See HYPERTENSION [7-2] MEDITERRANEAN DIET [7-4])

DIETARY SUPPLEMENTS

"An Emerging Risk To Public Health."

10-1 AMERICAN ROULETTE—CONTAMINATED DIETARY SUPPLEMENTS

In August 2009, the U.S. FDA reported many products containing a wide variety of undeclared active pharmaceutical ingredients. Most of them were labeled as "dietary supplements" (**DS**) . More than 140 contaminated products have been identified.

These represent only a fraction of the contaminated supplements on the market.

A recent National Health Interview Survey reported that about 114 million people—more than half the adult population of the USA –consume dietary supplements. The supplements, which include botanical products, vitamins and minerals, amino acids, and tissue extracts, are regulated by the FDA under the 1994 Dietary Supplement Health and Education Act (**DSHEA**). Before 1994, herbal products were considered food additives, and their manufacturers were required to show proof of safety. Since passage of the DSHEA, DS are presumed to be safe and can be marketed with very little oversight.

The DSHEA presents serious obstacles to the FDA's ability to detect and eliminate contaminated DS. A wide range of DS has been found to be contaminated by toxic plant material, heavy metals, or bacteria. Dozens of DS are contaminated with prescription medications, or drugs rejected by the FDA because of safety concerns. These potential hazardous ingredients have been detected in products marketed for patients with diabetes, high cholesterol, or insomnia. They are most frequently found in products that promise sexual enhancement, optimal athletic performance, and weight loss.

DS marketed for weight loss are consumed by an estimated 15% of U.S. adults.

Individuals and companies that manufacture and distribute these products are very smart. Their intelligence does not include any moral restraint. They will do anything to make a dollar. They must be aware of the potential harm.

Our local newspaper frequently publishes outrageous advertisements for:

"Powerful new diet pills"

"Regain 10-15 years of lost memory power"

"Success in pain relief in over 90%"

"A revolutionary new drug-free formula to regain youthful prostate function"

"Plankton to cure cancer"

Our national pharmacies also advertise these products and make them readily available.

In addition, many homeopathic products are advertised. And many drugs are made available by drug purveyors in Canada without a prescription.

The expenditure of the National Center for Complementary and Alternative Medicine (NCCAM), funded by Congress, is approaching one billion dollars. After 10 years, it has not proved effectiveness of any "alternative" method.

Researchers from the Universities of Exeter and Plymouth (UK) studied over 1300 randomized, controlled trials of herbal medicines. They found only 3 that were of sufficient quality to draw meaningful conclusions. These 3 trials showed no convincing evidence of benefit. Individual herbal medicines (European, Chinese, and Ayurvedic) have an extremely sparse evidence base. There is no evidence supporting use in any indication. (BMJ October 13, 2007: 335: 743)

University medical schools still teach CAM and support professors of CAM. In the USA, CAM and "integrative" medicine has been called "kindly medicine"-- one that takes the whole patient into account.

"The placebo effect can continue to fool scientists and patients alike."

Primary care physicians should publicize these comments as much as possible.

D-DIMER TEST **(See VENOUS THROMBOEMBOLISM [8-])**

FALL PREVENTION **(See VITAMIN D [10-6])**

HEALTHY LIVING:

The Potential For Preventing Morbidity And Mortality Through Healthy Living Is Enormous.

8-1 HEALTHY LIVING: ***Is the best revenge***

"Many of the major chronic diseases, such as cardiovascular disease (**CVD**), cancer, and diabetes, which together comprise the overwhelming burden of mortality, are in large part preventable."

This study examined the extent to which 4 major lifestyle factors are associated with reduced risk of developing 4 leading causes of morbidity and mortality

Entered a prospective cohort of men age 40-65 (n = > 9 000) and women age 35-65 (n = > 14 000) between 1994 and 1998. Mean age = 48.

Follow-up for a mean of 8 years. Endpoints = type 2 diabetes, myocardial infarction, stroke, and cancer.

Investigated 4 lifestyle factors dichotomized into 2 categories: smoking vs no-smoking; BMI < 30 vs BMI > 30; Physical activity > 3.5 hours/wk vs < 3.5 hours/wk; healthy diet vs no healthy diet. Healthy diet = value > median of the sum: fruits and vegetables, whole grain, and red meat. (Eating less red meat yielded a higher score.)

Overall, 2006 participants (9%) were clinically diagnosed as having 1 of the 4 study outcomes.

Outcomes:	No. of healthy lifestyle factors				
	0	1	2	3	4
No. of participants	924	5491	8206	6432	2100
No. of events	209	640	667	394	96
Events per 1000 person-years	32	15	10	8	6
Adjusted hazard ratio	1.00	0.51	0.37	0.28	0.22

Each healthy lifestyle was associated with a reduction in risk of any chronic disease. BMI under 30 exerted the largest reduction in risk, followed by never smoking, physical activity, and adherence to a healthy diet.

In this German cohort, only 9% of participants met criteria for all healthy factors. In the US population, as well, only a small fraction meets recommendations for multiple beneficial lifestyle behaviors.

Each of the 4 factors was associated with a reduction in risk. Each factor contributed to risk reduction, independently of the other factors.

"The message from our analysis . . . is clear—adopting a few healthy behaviors can have a major impact of the risk of morbidity." The participants with all 4 healthy lifestyle factors had a reduced risk of major chronic diseases of almost 80% compared with those with none.

Conclusion: Adhering to 4 simple healthy lifestyle factors can have a strong impact on prevention of chronic disease.

This is another study emphasizing the importance of life-styles in maintaining health. A primary responsibility of primary care is to encourage patients to adopt healthy lifestyles. If the general public maintained a favorable weight, ate a healthy diet, maintained physical fitness, and quit smoking, the

benefit on the nation's health would be tremendous, and concern about costs of national health care would vanish.

Now—How to do it?

HEADACHE (See CLUSTER HEADACHE [12-3])

HEART FAILURE

Maintenance Of Healthy Lifestyles Is Critical To Lowering Risk Of Heart Failure

7-1 RELATION BETWEEN MODIFIABLE LIFESTYLE FACTORS AND LIFETIME RISK OF HEART FAILURE

The concept of lifetime risk is important in public health practice. It is defined as the risk of ever developing a disease during one's lifetime.

Several predictors of HF can be influenced by modifiable lifestyle changes: maintaining healthy weight; not smoking; engaging in regular exercise; maintaining a healthy diet. This study examined the association between modifiable lifestyle risk factors and remaining lifetime risk of HF in a large cohort of men.

A prospective cohort study used baseline data from the Physicians' Health Study (1982-2008; over 20 000 individuals; mean age 53 at baseline) to examine the association between modifiable lifestyle factors and remaining lifetime risk of HF. All subjects were apparently healthy at baseline

The study considered 6 healthy lifestyle factors (**HLFs**), which were assessed periodically and dichotomized:

BMI: Under 25 vs overweight (25-29) or obese (30 and over)

Smoking: Never vs ever

Exercise; Regular (5 times a week or more) vs infrequent/ none

Alcohol intake: Moderate 5 drinks per week or more vs less than 5 drinks per week.

(Few drank > 2/day)

Consumption of breakfast cereals: One or more per week vs none

Consumption of fruits and vegetables: 4 or more servings per day vs fewer than 4.

Individuals could have 0 to 6 healthy lifestyles. Since very few men were in the 5 and 6 categories of healthy lifestyles, the investigators collapsed the upper 3 categories and referred to them as the 4 and over group.

Main outcome measure = lifetime risk of HF. Follow-up for 22 years.

Overall, the lifetime risk of HF was 14% at age 40. It remained constant through age 70. At age 80, lifetime risk was 11%. Remaining lifetime risk of HF was 2% to 4% higher in men with hypertension than in men without.

Lifetime risk of HF according to number of HLFs:

Those with 0 had a risk of over 20% for HF. Risks progressively fell to about 10% for those adhering to 4 or more. Each was associated with a lower lifetime risk of HF compared with the corresponding undesirable behavior.

Conversely, each added risk factor increased risk of HF. The lowest risk was observed in those with 4 or more HLFs—a reduction of 50% compared with those with 0. .

Conclusion: In this cohort of apparently healthy men, adherence to healthy lifestyles was associated with lower risk of HF.

As the article states, incidence of HF in the general population is much higher than in this physician's group.

A number of articles regarding benefits of healthy lifestyles are appearing in the journals.

Repeatedly encouraging patients to adopt healthy lifestyles will, if successful, be a necessary step in achieving and maintaining lower costs of our proposed changes in health care. This can be accomplished only by long- time primary care.

"Suggesting A New Avenue For Therapeutic Exploration"

12-7 ANEMIA AND IRON DEFICIENCY--NEW THERAPEUTIC TARGETS IN HEART FAILURE?

Anemia in patients with heart failure (**HF**) ranges from 10% for patients with mild HF, to over 40% in patients with advanced HF

Anemia in HF has been associated with old age, diabetes, chronic renal dysfunction, more advanced HF, lower peak exercise capacity, and worse health-related quality-of-life metrics.

Anemia is a powerful predictor of hospitalization and survival in chronic HF.

A complex interaction between impaired cardiac performance, activation of neurohumoral and inflammatory responses, drug effects, renal dysfunction, and bone marrow hypo-responsiveness appears to contribute to the anemia.

Iron deficiency may also be due to the effect of HF on absorption of dietary iron. Gastrointestinal malabsorption, long-term aspirin, and uremic gastritis may add to iron deficiency.

Chronic iron deficiency may, by itself, cause ultrastructural alterations in cardiomyocytes.

Since anemia is closely associated with poor clinical outcomes among patients with HF, it is logical to consider whether correcting anemia may improve functional capacity and survival.

A study in this issue of NEJM (*see the full abstract for citation*) reported the effect of intravenous iron given to patients with mild to moderate HF.

The administration of iron convincingly improved self-reported Patient Global Assessment and NYHA functional class; 50% reported they were much or moderately improved as compared with 23% in the control group. The degree of improvement was similar in patients without anemia and those with anemia.

Patients receiving iron also improved their 6-minute walk distance by 30 m.

I abstracted this article because it presents an entirely new aspect of treatment of HF. Primary care clinicians, keep it in mind

HIGH-DENSITY LIPOPROTEIN CHOLESTEROL (HDL)

HDL-c is Inversely And Independently Associated With A Reduction In CV Events.

10-5 EVALUATING THE INCREMENTAL BENEFITS OF RAISING HIGH-DENSITY LIPOPROTEIN CHOLESTEROL LEVELS DURING LIPID THERAPY AFTER ADJUSTMENT FOR THE REDUCTIONS IN OTHER BLOOD LIPID LEVELS.

This study analyzed data from individuals treated with lipid-modifying therapy in the Framingham Offspring Study from 1973-2003, focusing only on those individuals who started lipid therapy between the 2nd and 6th visits.

It tested the hypothesis that an elevation in HDL-c levels is inversely and independently associated with a reduction in CV events.

Plasma lipid levels were determined for each individual before therapy was started, and at follow-up visits.

Determined change in HDL-c levels after lipid-modifying therapy for each individual.

Patient characteristics:	Quartiles of change in HDL-c levels (mg/dL)			
	-36 to -3	-2.7 to + 2,3	+2.5 to + 7.0	+ 7.8 to + 35
Number of patients	117	108	121	108
Untreated HDL-c level (mean)	48	40	39	40
Average treated HDL-c	41	40	44	53
Untreated LDL-c level (mean)	171	160	160	160
Average treated LDL-c	126	122	125	127

Untreated TG (mean mg/dL)	209	212	273	293
Change in TG (mg/dL)	-23	-28	-94	-144
No.of events (%)	31 (26)	17 (16)	19 (16)	12 (11)

During an average follow-up of 8 years, 79 individuals experienced a CV event. After adjustment for pretreatment HDL-c levels, age, and sex, the hazard ratio (**HR**) for CV events associated with a 5 mg/dL increase in HDL-c was 0.80.

Overall, a 1% increase in HDL-c level was associated with a 2% drop in CV risk. The lower the pretreatment LDL-c, the greater the risk reduction associated with an increase in HDL-c level.

In this analysis, of individuals starting pharmacotherapy for dyslipidemia, there was an inverse relationship between changes in HDL-c levels and CV events. The greater the increase in HDL-c level, the lower the CV risk—an observation that persisted after adjustment for changes in LDL-c and triglycerides and other potential confounders.

Conclusion: Although the benefits of raising HDL-c levels remain to be confirmed in randomized trials, it appears the modest changes in HDL-c levels resulting from treatment with commonly used lipid drugs are associated with a reduction in CV risk, independent of the effects of other lipid measures.

HIP FRACTURE

Rates And Subsequent Mortality Among Persons Over Age 65 Have Declined

10-8 INCIDENCE AND MORTALITY OF HIP FRACTURES IN THE UNITED STATES

This observational study of patients age 65 and older examined the trends in hip fracture (**HF**) incidence and resulting mortality over 20 years in a 20% sample of the US Medicare claims. 1985-2005.

Identified over 786 000 HF in patients discharged from acute care hospitals.

Of the 786 717 hip fractures, 77% occurred in women.

Annual mean number of HF:

957 per 100 000 in women

414 per 1000 000 in men.

The median hospital stay decreased from 12 days to 5 days. The discharge destination changed from going home with self-care (34%) to only 5%. In the last years, 53% were discharged to a skilled nursing facility.

In women, the incidence of hip fractures increased by 9% from 1986 to 1995. It then steadily declined by 25% from 1995 to 2005, In men from an increase of 16% to a decline of 19%.

In women, over the entire study period, the adjusted 30-day mortality decreased from 5.9% to 5.2%; 180-day mortality decreased from 16.8% to 14.3%; 360-day mortality from 24% to 22%. In men the decrease was somewhat larger.

Use of bisphosphonates in women gradually increased over time, with use by few in 1996 to 20% in 2005. Relatively few men took bisphosphonates. Selective estrogen receptor moderators (SERM) use also increased to about 5%. Estrogen use peaked about 2000, and declined thereafter to less than 10%.

This analysis over 20-years reveals two distinct eras: 1) 1986-1998 HF incidence was increasing, but mortality after HF was falling; 2) 1998-2006 the incidence of HF fell, but mortality remained essentially unchanged.

After 1996, there was a larger decrease in HF in women (decline of 25%) than in men.

The reason for the decline in incidence is not clear. It corresponds temporally with the market release and increasing use of bisphosphonates. (However, a causal relationship has not been demonstrated.) This trend is not likely to explain the entire decline in incidence. HF incidence also fell in men, despite low use of bisphosphonates.

Lifestyle changes may contribute to the decline: calcium and vitamin D supplementation; avoidance of smoking; exercise; moderating alcohol use. And public and physician education and awareness of osteoporosis and fragility fractures.

Surgical and medical management of HF has improved over the past 20 years: improved surgical devices and replacement; earlier weight bearing exercise and improved mobilization: better use of prophylactic antibiotics; increased rates of discharge to non-acute health care settings (rather than to home).

Recurrent fracture is an important risk factor for premature mortality. Increased use of bisphosphonates may reduce incidence of recurrence.

Conclusion: In the US, HF rates and subsequent mortality among persons over age 65 have declined. Co-morbidities among the elderly have increased.

Hip fracture is largely a disease of older women. As women live longer, incidence of HF in those over age 85 is increasing. Prevention rests largely on primary care.

Many changes have improved prognosis. I like to believe that use of bisphosphonates and vitamin D and calcium supplementation have played a role. Has the growing prevalence of obesity also lowered risk of HF?

HISTAMINE BLOCKER **(See PEPTIC ULCER [7-6])**

H1N1 FLU

"Containment Is No Longer Possible"

7-9 A/H1N1 INFLUENZA UPDATE (July 25 2009) From the UK Health Protection Agency (HPA)

This up-to-date review asks:

A. What more do we know compared with 2 months ago?

B. Has advice to healthcare professionals from the HPA changed since the WHO announced pandemic alert 6 in June?

C. What are the latest predictions on how serious this virus is?

D. How are current arrangements for administering oseltamivir working?

E. Is it worth wearing a face mask?

F. What are the likely arrangements for distribution of the vaccine?

G. Should pregnant health care workers deal with patients with flu?

H. Has AH1BN1 mutated?

I. Is AH1N1 more likely to infect the lungs?

J. Where can up-to-date information be accessed?

http://pandemicflu.bmj.com

www.dh,gov.uk

www.hpa.org.uk

www.rcgp.org.uk *Please read the full abstract*

HUMAN PAPILLOMA VIRUS

"The Only Efficient Way To Stop The Virus Is To Vaccinate The Other Half Of The Sexually Active Population; Boys And Men."

7-7 HPV VACCINE FOR ALL

A randomized trial reported in *Lancet* this month reports efficacy of a bivalent HPV vaccine (types 16 and 18 with an aluminum adjuvant in 9000 women age 15-25) for the reduction of high-grade cervical intraepithelial neoplasia (CIN2+/CIN3+),

Over 3 years, CIN2+ associated with HPV 16/18 in those receiving vaccine, vs controls, was reduced by 93%, and CIN2+ associated with HPV 31/33/45/52/58 was reduced by 53% compared with controls.

The neutralizing antibody response to HPV vaccines exceeds the natural immune response to infection with the virus, but life-long immunity in unlikely, making need for a booster probable.

The primary public heath goal is to stop the spread of infection, and ultimately disease. “The only efficient way to stop the virus is to vaccinate the other half of the sexually active population; boys and men.” In clinical trials, males show an immune response similar to that of women.

The lifetime risk of HPV infection in the sexually active population is 80% to 90%. Although the virus is eliminated from the body within 2 years in 80% of those infected, infections are more likely to become persistent in older individuals and those with compromised immunity.

“Women have shouldered responsibility for contraception since its inception. The goal to eradicate sexually transmitted carcinogenic viruses can be jointly carried by both women and men, and could be accomplished within a few decades.”

We need much more information about safety, especially long-term, and effectiveness long-term before application can be made to males.

Perfect Protection for 6 Years, And Likely Longer

12-2 SUSTAINED EFFICACY AND IMMUNOGENICITY OF THE HUMAN PAPILLOMA VIRUS (HPV)-16/18 AS0-4-ADJUVATED VACCINE

Infection with oncogenic human papilloma virus (**HPV**) is the necessary cause of cervical cancer (**CC**). Fifteen oncogenic types have been identified. Most (70%) CC is caused by types related to HPV 16 and 18. Other common types are 31, 33, 45, 52, and 58.

Vaccines for HPV have to provide long-term protection, since the risk of acquiring an infection begins with sexual debut and continues through life.

Women with a naturally acquired infection remain at risk for a new infection with the same HPV type possibly because antibody concentrations after natural infection are low and do not offer sufficient protection.

The HPV 16/18 ASO-4 vaccine used in this study is adjuvated by a system comprised of aluminum salt and the immunostimulatory molecule ASO4. This adjuvated vaccine produces consistently higher antibody titers, which are sustained over a longer period, together with a higher frequency of memory B cells than do the same antigens adjuvated with aluminum only.

This multicountry study (27 sites), begun in 2003 and continued through 2007, entered healthy young women (age 15-25; n = 776). All had normal cervical cytology, were HPV 16 and 18 seronegative, and were DNA negative by PCR for 14 oncogenic HPV types in their cervical cells.

Randomized, double-blind to:

1) Three doses of 16/18 adjuvated vaccine, or

2) Placebo

Mean follow-up = 5.9 years; maximum follow-up = 6.4 years.

Infection with 16/18:

	Vaccine (n = 401)	Placebo (n = 373)
Incident infection	4	70
6-month persistent infection	0	34
12-month persistent infection	0	20

(The vaccine was considered 100% effective against persistent infection with 16/18. This was despite recurrent exposure to the viruses over 6 years.)

Cytology: Associated with 16/18

	Vaccine (n = 481 to 505)	Placebo (n = 470 to 497)
CIN 1+	0	15
CIN 2+	0	9

(The vaccine was considered 100% effective against development of CIN.)

There was also some evidence of effectiveness against other types of HPV.

Incident infection (6 years)	16/18 Vaccine	Placebo
HPV type 31	13	30
HPV type 45	5	21

Immune response to vaccine: Neutralizing antibodies and IgG antibodies for 16 and 18 remained remarkably stable over 6 years at 5 to 13 times higher than the immunity produced by natural infections.

Safety: The vaccine was well tolerated. A similar number of women in both the vaccine group and the placebo group reported adverse events. No serious event was judged to be related or possibly related to vaccination. Over 130 pregnancies occurred in both groups without any difference in outcomes.

Although 16/18 cause roughly 50% of high grade squamous intraepithelial lesions, vaccine efficacy reached 72% against any CIN 2+, an indication that the vaccine is able to confer some protection beyond 16/18.

Because the incidence of CC peaks on average more than 30 years after adolescence, vaccine has to confer protection for many years. Six years of protection is the longest time span so far.

“We expect protection to continue for many more years.”

An excellent study! Detailed and convincing. This is an important step forward.

Even though CIN is a substitute outcome for CC, I believe it is a strong one.

It appears that the adjuvated vaccine will produce long-lasting immunity. Perhaps a booster will be required in 20 years or so.

Now the problem is to make HPV vaccine available world wide, where it is most needed

We continue to face the question about immunizing males as well as females.

The Advisory Committee on Immunization Practices (ACIP):

The FDA has approved both the bivalent (16, 18) and the quadrivalent vaccine (6, 11, 16, 18)

The latter also protects against genital warts.

There have been no published head-to-head studies between the two vaccines comparing effectiveness and duration of protection against cervical neoplasia and precancerous lesions

The vaccine is recommended for females at age 11 to 12 with catch up vaccination through ages 13 to 26.

Ideally, the vaccine should be administered before sexual debut but if not, women should still be vaccinated. Complete vaccination consists of three doses, the second at 1 month, the 3rd at 6 months.

Vaccine may be given to women with a history of an abnormal Pap smear, or a positive HPV DNA test, as these conditions are not evidence of prior infection with all HPV vaccine types.

The ACIP added a permissive use of the quadrivalent vaccine in males.

Annals Internal Medicine January 5,2010; 152: 36-38

HYPERTENSION

The Potential To Prevent A Large Proportion Of New-Onset Hypertension

7-2 DIET AND LIFESTYLE RISK FACTORS ASSOCIATED WITH INCIDENT HYPERTENSION IN WOMEN

Just 37% of individuals with hypertension in the USA have controlled BP; a proportion that increases to 57% with drug intervention.

The second Nurses' Health Study evaluated the association between combinations of low-risk lifestyle factors and risk of developing hypertension during a 14 year period.

Considered six modifiable low-risk lifestyle risk factors:

BMI < 25

Vigorous exercise daily (mean of 30 minutes)

A high score of the DASH diet (Response to a food frequency questionnaire.)

Modest alcohol intake (up to 10 g/d)

Use of non-narcotic analgesics (NSAIDs, aspirin, and acetaminophen) less than once weekly

Intake of 400 ug/d of supplemental folic acid or more.

Follow-up through 2005 (to mean age 50). Main outcome = adjusted hazard ratios for incident self-reported hypertension and population attributable risks of hypertension (**PARs**)

Specific groups of 3, 4, 5, and 6 risk factors were associated with progressively lower HRs of developing hypertension:

	HR	PAR (%)*
3 Highest DASH quintile, daily vigorous exercise, BMI < 25	0.46	53
4 The 3 above + alcohol 0.1 – 10 g/d	0.42	58
5 The 4 above + analgesic use < 1 day per wk	0.28	72
6 The 5 above + folic acid supplementation (only 0.3% of women)	0.22	78

(* Population attributable risk. The % of women who would have avoided hypertension if all women had been in the low risk groups.)

Hypothetically, compared with women who maintained no beneficial lifestyle factors, risk of hypertension in women who maintained 5 healthy lifestyle factors for 10 years would be lowered by 72%.

Combinations of modifiable risk factors were associated with a dramatically reduced incidence of new-onset hypertension over 10 years. If these associations were causal and independent, lifestyle modification could have the potential to prevent a large proportion of new-onset hypertension occurring in young women,

In this study, BMI was the most powerful predictor of incident hypertension, and the largest single contributor to the hypothetical PAR. Although multiple low-risk factors were significantly associated with lower risk among normal weight and overweight individuals, there was no association among obese women (BMI > 30). Obese women might not benefit from other low-risk behaviors unless weight loss is also addressed.

The study did not have information on plasma 25-OH-vitamin D. Low levels have recently been demonstrated to be related to risk of hypertension, as well as high waist circumference.

Conclusion: Adherence to low-risk dietary and lifestyle factors was associated with significant reductions in the incidence of self-reported hypertension. It could have the potential to prevent a large proportion of new-onset hypertension among young women. This would have major public health benefits.

The reference to vitamin D is interesting. Interest in possible beneficial effects persists. Most people, at least in winter, who live at higher latitudes are deficient. Supplement the diet with 1000 to 2000 units daily. It is inexpensive.

Without weight loss, obese women derive no benefit from maintaining healthy lifestyles.

Lowering risk factors will be a major component of the proposed revision of health care in the US. This would require a sea change in habits of the population. Can this be accomplished? I believe only by continuous medical care by primary care in a medical home. Primary care clinicians must be role models, and abide by all facets of healthy living.

If a major proportion of citizens would maintain healthy lifestyles, I believe we would have no more concerns about costs of universal health care coverage.

I do not recall hearing about any relation between aspirin, acetaminophen, and folic acid to risk of hypertension.

Decreased The Likelihood Of Left Ventricular Hypertrophy

8-5 USUAL versus TIGHT CONTROL OF SYSTOLIC BLOOD PRESSURE IN NON-DIABETIC PATIENTS WITH HYPERTENSION

The relation between the incidence of stroke or coronary heart disease (**CHD**) is continuous at all ages. A reduction in systolic BP has explained most of the treatment benefit in patients with hypertension. Guidelines now recommend that BP be reduced to values less than 140/90 or 140/85.

This multicenter, open-label randomized trial in Italy entered 1111 non-diabetic patients with hypertension. (Present guidelines already recommend tight BP control in diabetics.) All were over age 55 and had a systolic BP of 150 or higher. (Mean BP = 163/90.) Patients had at least one additional risk factor. It tested the hypothesis that tight control (systolic < 130) vs usual control (systolic < 140) would be beneficial in non-diabetic patients with hypertension.

Used open-label agents to reach targets. (Various combinations of a diuretic, ACE inhibitor, angiotensin blocker, calcium blocker, alpha-1 blocker, and beta-blocker.)

Primary end-point = left ventricular hypertrophy determined by ECG at 2 years.

Secondary outcome = composite of all-cause mortality, fatal or non-fatal stoke , TIA, congestive heart failure, new-onset atrial fibrillation, angina pectoris, aortic dissection, occlusive peripheral vascular disease, and renal failure.

Baseline characteristics (means): age 67; BMI 28; BP 163/90; current cigarette smoking 22%; dyslipidemia 77%; women 59%. Patients were already taking a variety of drugs.

Outcomes at 2 years	Usual group	Tight group

BP decrease	28/11	31/12
BP difference between groups	3.8/1.5	
Achieved systolic BP < 130	27%	72%
Presence of LVH on ECG (%)		
Baseline	21	22
2 years	17	11
Composite secondary endpoint (%)	9	5

"Setting a systolic target of less than 130 mm Hg instead of the usual 140 mm Hg in patients with treatment-resistant systolic hypertension was feasible and well tolerated."

Conclusion: Tight control of systolic BP to less than 130 in non-diabetic patients with at least one additional risk factor decreased the likelihood of left ventricular hypertrophy determined by ECG, and clinical events, as compared with usual control to less than 140.

Note that these patients had other risk factors to address. Primary care would address them all simultaneously, not BP alone.

Setting "normal" values for BP and many other risk markers is arbitrary and artificial.

There is good evidence that at each baseline systolic, lowering systolic BP from any reasonable starting point will reduce relative risk of adverse effects of hypertension by a constant %, , and absolute risk by an amount which decreases with each step. See "Use of Blood Pressure Lowering Drugs in the Prevention of Cardiovascular Disease" A Meta-analysis of 147 Randomized Trials in the Context of Expectations from Prospective Epidemiological Studies BMJ May 23, 2009; 338: 1245-53. Abstracted in Practical Pointers for Primary Care Medicine May 2009 [5-1]

I believe primary care clinicians should lower systolic BP to as low a level as tolerated by the patient (but not below 120 systolic). Older patients should be concerned about only their systolic pressure, removing the confusion about systolic/diastolic. This may increase understanding and compliance. Therapy should consist of the lowest dose of a combination of several drugs given for the least number of times daily, preferably combined into one "pill". Generic drugs are usually all that are needed, and can be bought at low cost.

"A Diuretic Should Be Part Of Any Multidrug Regimen."

11-4 FIFTY YEARS OF THIAZIDE DIURETIC THERAPY OF HYPERTENSION

"Thiazides and thiazide-like diuretics have remained a cornerstone in the management of hypertension for more than half a century since their introduction in 1958. Very few agents used for the treatment of any disease can boast such staying power."

This is a testament both to the efficacy and safety of these compounds, and to the relevance of salt and volume contraction to the management of essential hypertension.

This 50th anniversary article reviews the history of the discovery and development of thiazides, mechanism of action, important trials documenting their role in prevention of cardiovascular disease, and the possible few limitations to the use of diuretics.

Please read the full abstract.

I abstracted this article with pleasure. I lived and practiced though the entire history of thiazide development. Indeed, I remember when weekly mercuhydrin injections were standard therapy for congestive heart failure.

I believe the development of thiazides was one of the major advances in medicine in the past century.

The article repeats the importance of BP control in patients with diabetes.

Chlorthalidone and hydrochlorothiazide are very inexpensive. Some pharmacies sell them for $10 for a 3-month's supply.

The benefit / harm - cost ratio of thiazides is very high.

LEMIERRE SYNDROME **(see PHARYNGITIS [12-8])**

LIFESTYLE FACTORS **(See HEART FAILURE [7-2])**

LIPIDS

No Need To Fast; No Need To Measure Triglycerides

11-3 MAJOR LIPIDS, APOLIPOPROTEINS, AND RISK OF VASCULAR DISEASE

Uncertainty persists about the merits of measurement and modification of triglycerides with the risk of vascular disease. It is not clear to what extent these relationships depend on cholesterol levels or vary with the fasting state.

This study assessed the relationship between major lipids and apo-lipoproteins and vascular risk.

Individual records were supplied on over 302 000 people in 22 countries (2.79 million person-

years; mean age 59; 57% male) from 68 long-term prospective studies. No person had known vascular disease initially. At baseline, all had determinations of total cholesterol, HDL-cholesterol (HDL-c), and triglycerides (TG), and conventional risk factors (age, sex, smoking, diabetes, systolic BP, and body mass index).

Twenty-two studies (> 91 000 participants) had information on apo A-1 and apo B, and 8 studies (> 44 000 participants) had directly measured low-density cholesterol (LDL-c) values.

During 2.79 million person-years of follow-up there were 8857 non-fatal myocardial infarctions (MI), 3928 CHD deaths, 2534 ischemic strokes, and 513 hemorrhagic strokes..

Calculated non-HDL-c by subtracting HDL-c from total cholesterol. This measure encompasses low-intermediate- and very-low density lipoprotein cholesterol.

Hazard ratios for CHD of apo-lipoproteins compared with non-HDL-c

A. Apo-B compared with non-HDL-c

The mean lowest quintile level of apo B = 85mg/dL; the highest = 137

As apo B (*the Bad cholesterol*) rose, the hazard ratio for CHD increased from 1.0 to 2.0

The mean lowest quintile non-HDL-c = 125; the highest = 198

As non-HDL-c rose, the hazard ratio increased from 1.0 to 2.0

(Ie, the two were equally predictive of increasing harm as levels rose.)

B. Apo A1 compared with HDL-c

The mean lowest quintile level of apo A1 = 126 mg/dL; the highest = 178

As apo A1 increased the hazard ratio for CHD decreased from 1.0 to 0.7

The mean lowest quintile level of non-HDL-c = 125; the highest = 196

As HDL-c increased, the hazard ratio for CHD decreased from 1.0 to 0.7

(Ie, the two were equally predictive of increasing benefit as levels rose.)

Similar relationships were calculated for ischemic stroke. The absolute risks and benefits were much lower, but still in the same direction.

“The current analysis of more than 300 000 people has demonstrated that lipid assessment in vascular disease can be simplified by measurement of either cholesterol levels or apolipoproteins without the need to fast and without regard to triglycerides.”

In contrast with previous finding based on much less data, triglyceride concentration was not independently related with CHD risk after controlling for HDL-c, non-HDL-c, and other standard risk factors. “Hence, for population-wide assessments of vascular risk, triglyceride measurement provides no additional information about vascular risk given knowledge of HDL-c and total-c levels.”

Concentrations of HDL-c and non-HDL-c were each strongly associated—in opposite

directions—with CHD risk.

HDL-c and non-HD-c levels were largely independent of each other as well as from triglyceride concentrations and other risk factors. “Hence, whereas prevailing therapeutic strategies focus on lowering LDL-c (or approximately analogously, non-HDL-c) the current findings suggest that therapy directed at *raising* HDL-c as well as *lowering* non-HDL-c may generate substantial additional benefit.”

“The current prospective data contrast sharply with those of some large retrospective case-control studies that reported that apolipoproteins have much stronger associations with CHD risk than cholesterol levels.”

Conclusion: Lipid measurements in vascular disease can be simplified by measurement of total-c and HDL-c or apolipoproteins without the need to fast and without regard to triglyceride.

This study was much more complicated than I have indicated. It included many statistical applications.

I believe I have captured the results and the meaning of the study. The study was large and included many countries. This would favor generalizability.

The message is:

Aim for a ratio of HDL-c to non-HDL-c as high as possible. (The study did not calculate ratios.)

No need to fast or measure triglycerides.

This simplifies calculation of risks and benefits of therapy and adds to convenience of testing.

MAMMOGRAPHY

“All Screening Programs Do Harm. Some Do Good As Well.”

11-1 EFFECTS OF MAMMOGRAPHY SCREENING UNDER DIFFERENT SCREENING SCHEDULES: Model Estimates of Potential Benefits and Harms.

This study was based on 6 models of breast cancer (**BC**) incidence and mortality in the U.S. These models were ideally suited for estimating the effect of screening under a variety of policies, and for facilitating comparisons of strategies. The models were developed independently\y by prestigious Medical Schools and Universities, and Cancer centers.

They predicted a cumulative probability of BC mortality developing over a woman’s lifetime, starting at age 40 vs starting at age 50

They also predicted probability of death from BC from annual screening vs biennial screening (every 2 years).

Without screening, the median probability of dying from BC after age 40 is 3%. If a particular screening strategy leads to a 10% reduction in BC mortality, then the probability of BC mortality would be reduced to 2.7%, or 3 deaths prevented per 1000 women screened. [10% X 3 = 0.3%; 3% - 0.3% = 2.7%]

A. Comparison of different STARTING ages:

1) Starting at age 40 averted 6.2 cancer deaths per 1000 screened.
2) Starting at age 50 averted 5.4 cancer deaths per 1000 screened.
3) One additional life saved per 1000 screened at the expense of 470 false positives and recalls, 33 unnecessary biopsies, and an additional 4000 mammograms

B. Comparison of ANNUAL screening vs screening every 2 YEARS:

1) Screening every year from age 40 to age 69 resulted in a reduction of cancer mortality of 8.3 per 1000 screened
2) Screening every 2 years from age 40 to age 69 resulted in a reduction in cancer mortality of 6.2 pre 1000 screened.
3) A difference of 2 lives saved per 1000 screened.
4) This advantage was at the expense of 1000 false positives and recalls, 70 unnecessary biopsies, and 14 000 more mammograms.

C. Comparison of different STOPPING ages:

1) Screening every 2 years from age 50 and stopping at age 69 averted 5 deaths for every 1000 screened.
2) Screening every 2 years from age 50 and stopping at age 79 averted 9 deaths for every 1000 screened.
3) Four additional deaths per 1000 screened were averted by extending screening to age 79 at the expense of 230 false positives and call backs, 16 unnecessary biopsies, and 3000 mammograms.

"The conclusion of this modeling analysis is that biennial intervals are more efficient and provide a better balance between benefits and harms than annual intervals."

Substantial increases in false-positive results and unnecessary biopsies were associated with annual intervals. These harms are reduced by almost 50% with biennial intervals.

Slow-growing tumors are much more common than fast-growing tumors. The ratio of slow- to fast-growing tumors increases with age, so little survival benefit is lost between screening every 2 years vs every year.

Screening strategies that include an upper age limit beyond age 69 remain efficient albeit with

low incremental gains over strategies that stop at earlier ages, and with greater harms.

These models provide estimates of the average benefits and harms expected across a cohort of women. They do not reflect personal data for individuals.

The models do not capture differences in outcomes among certain subgroups such as women with BC genetic susceptibility, women who are sicker or healthier than average, or black women.

The models do not capture the morbidity associated with surgery for screen-detected disease or decrements in quality of life associated with false positive results, living with earlier knowledge of cancer diagnosis and overdiagnosis.

The study did not include costs.

Conclusion: Starting mammography screening at age 50 instead of age 40, and every 2 years instead of every year achieves most of the benefits with much less harm. Decisions about the best strategy depend on individual objectives, and the weight placed on harms, benefits, and resource considerations.

To put this into perspective helping women to choose, I believe we can inform them that the best scientific knowledge indicates:

By choosing to start screening mammography at age 50 instead of age 40, you will increase risk of death from BC by 1 in 1000. This will be at the expense of 4 additional mammograms, and 470 chances in 1000 of a false positive and call-back, and 33 chances in 1000 of receiving a biopsy.

By choosing screening every 2 years instead of every year, you will increase your chances of dying from BC by 2 in 1000. This will reduce the number of mammograms and false positives by about half, and decrease the number of biopsies.

By extending screening from age 69 to age 79, you will reduce the chances of death from BC by 4 in 1000 screened. This will be at the expense of 5 extra mammograms, increasing the chance of false positives by at least 2 in 10, and increasing the number of unnecessary biopsies.

The study did not address monetary costs.

"Thus, The Recommendation Against Routine Screening At Ages 40-49"

11-2 SCREENING FOR BREAST CANCER: U.S. PREVENTIVE TASK FORCE (USPSTF) RECOMMENDATION STATEMENT

This is an update of the 2002 USPSTF recommendation statement on screening for breast cancer (**BC**) in the general population. The USPSTF makes recommendations about preventive care services for patients who have no recognized signs or symptoms of the target condition.

The USPSTF recognizes that clinical or policy decisions involve more considerations than the body of evidence alone. Clinicians should understand the evidence, but *individualize decision making* to the specific patient or situation.

Summary of recommendations and evidence:

1) The USPSTF recommends against *routine* screening mammography in women age 40-49. The decision to start screening before age 50 should be an individual one, taking patient context into account, including the patient's values regarding specific benefits and harms.
2) The USPSTF recommends screening *every 2 years* for women age 50-74.
3) The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening in women age 75 and older.
4) The USPSTF recommends against teaching breast self-examination.
5) The USPSTF concludes the current evidence is insufficient to assess the additional benefits and harms of clinical breast examination *beyond screening mammography* in women age 40 and older.
6) The USPSTF concludes that the current evidence of benefits and harms of either digital mammography or magnetic resonance mammography (MRI) instead of film mammography is insufficient.

The USPSTF reasoned that the additional benefit gained by starting at age 40 rather the age 50 is small, and that moderate harms from screening remain at any age. Thus, the recommendation against routine screening at ages 40-49.

Potential harms of mammography:

False positive results are common and lead to additional imaging, and unnecessary biopsy. (False negative results occur at a relatively low rate for all ages.)

Anxiety, distress, and other psychosocial effects can occur, but usually are transient.

Overdiagnosis can occur when screening detects early-stage invasive BC or ductal carcinoma in situ (DCIS) in a woman who is likely to die from another cause before the BC would be clinically detected. Over diagnosis can also occur if a detected DCIS or other early-stage lesion never progresses to invasive cancer.

Unnecessary earlier treatment can occur at any age when screening detects a slower-growing cancer that would have eventually become clinically evident, but would never have caused death.

Radiation exposure may increase risk of BC, but usually at much higher doses than those

used in mammography, although regular mammography could contribute to cumulative radiation doses from additional imaging.

I struggled to abstract the 2 articles on screening for BC in a concise and meaningful way.

The report from the USPSTF raised considerable ire among some women, particularly those in their 40s in whom BC had been detected by mammography. They completely misread the recommendation. They raised the specter of "rationing" by interpreting it to mean that the USPSTF recommended against screening between ages 40-49. The USPSTF did no such thing. It recommended against routine screening at this age. (Ie, against universal screening—against automatically recommending screening for everyone beginning at age 40.)

Physicians and patients should consider the individual's decisions about screening after she has been adequately informed about harms as well as benefits. Some women are so fearful of BC that they will request frequent screening beginning at an early age. Their decisions should be honored.

The recommendations against breast self-examination, I doubt will persuade those who do self-examine to stop.

The recommendation about examination of the breasts in the physician's office during a routine physical examination pertains only if a mammogram is not contemplated. I presume most primary care clinicians will continue to examine the breasts during a routine check up.

Regarding DCIS, I believe that most young women would opt for surgery and not temporize by watchful waiting. The risk of progression to malignancy is too great.

MEDICAL IMAGING **(See RADIATION [8-8])**

MEDITERRANEAN DIET

Moderate Consumption of Ethanol, High Intake Of Vegetables, Fruits And Nuts, Olive Oil, And Legumes.

7-4 ANATOMY OF HEALTH EFFECTS OF MEDITERRANEAN DIET

This study investigated the relative importance of individual components of the Mediterranean diet (**MD**) associated with the inverse association between adherence to the diet and mortality.

Entered a population-based cohort of over 23 000 men and women in Greece between 1994 and 1997. All were free of cancer, coronary heart disease, or diabetes. Follow-up for a mean of 8.5 years

Assessed dietary intake by a food frequency questionnaire during the year prior to enrollment:

Vegetables *

Legumes *

Fruits and nuts *

Fish and seafood *

Cereals *

High monounsaturated to saturated fat ratio *

Ethanol * (For men 10 g a day to less than 50 g a day; Women 5 g and 25 g)

Dairy **

Meat and meat products **

(* beneficial ** not beneficial)

Assessed conformity to the traditional MD with a 10-unit scale based on the 9 variables.

During follow-up, 1075 deaths from any cause occurred.

MD score	Deaths	% of cohort
0-4	652	5.1
5 or more	423	4

Each 2 unit increase in the MD score was associated with a mortality ratio of 0.86. (14% decrease)

Among the 7 presumed beneficial components of the diet, high consumption of all but fish and seafood was inversely associated with mortality.

For meat and meat products and dairy, there was a positive relationship with mortality, which approached statistical significance.

The contribution to the association with lower mortality was largest for moderate consumption of ethanol (24%). Followed by low consumption of meat and meat products (16%), and high consumption of vegetables (16%). Followed by high consumption of fruits and nuts,, high mono-unsaturated to poly-unsaturated fat ratio, and high consumption of legumes (each contributing 10-14%). High consumption of cereals and low consumption of dairy products contributed less (5%).

Close adherence to the traditional MD diet, as indicated by the MD score, was associated with a statistically significant lower overall mortality.

Intake of up to 50 g of ethanol daily is not "moderate". I would advise no more than one glass of wine daily. I would limit intake to one drink daily.

Delayed The Need For Drug Therapy And Led To More Favorable Changes In Glycemic Control And Coronary Risk Factors

9-3 EFFECT OF A MEDITERRANEAN –STYLE DIET ON THE NEED FOR ANTI-HYPERGLYCEMIC DRUG THERAPY IN PATIENTS WITH NEWLY DIAGNOSED TYPE-2 DIABETES

Lifestyle intervention studies have demonstrated large reductions in risk for type-2 diabetes (**DM-2**).

The American Diabetes Association (**ADA**) recommends that patient with newly diagnosed DM-2 be treated with pharmacotherapy as well as lifestyle changes. The rationale for combined therapy is that each form of treatment alone is imperfect. Lifestyle changes are often inadequate because patients do not lose weight, or regain weight, or that their diabetes worsens independently of weight.

This randomized trial compared with effectiveness, durability, and safety of a low-carbohydrate Mediterranean diet (**MD**) vs a low-fat ADA diet in patients with newly diagnosed DM-2.

Between 2004-2008 followed 215 overweight patients (mean age 52) with newly diagnosed DM-2. None had been treated with drugs. All were sedentary and had a stable weight over the past 6 months. At baseline, mean BMI = 30. HbA1c = 8%. All received education emphasizing the importance of a healthy diet and physical activity. (**PA**)

Randomized subjects to 1) a low-carbohydrate Mediterranean diet (**MD**), or 2) a low-fat ADA diet.

Mediterranean diet: rich in vegetables and whole grains, and low in red meat. Energy was restricted to 1500 kcal/d in women and 1800 in men, with a goal of a carbohydrate content of less than 50% of daily energy; and less than 30% of calories as fat. (The main source of fat was olive oil.)

ADA diet: Based on ADA guidelines. Rich in whole grains and reduced fat, sweets, and high-fat snacks. No more than 30% of energy from fat, and no more than 10% as saturated fat. Calorie restriction the same as the MD.

After 4 years:	MD	ADA-diet
Requiring drug treatment (%)	44	70 (Almost all with persistent HbA1c >7%)
BMI	- 1.2	-0.9
Waist circumference (cm)	- 3.0	-2.6
HbA1c (%)	-0.9	-0.5

The MD group also had slight advantages in serum insulin, lipids, systolic BP, total energy intake, and carbohydrate and fat intake.

Participants in both groups increased the time spent being physically active, with no statistical significant difference between groups.

Conclusion: Compared with an ADA low-fat diet, a low carbohydrate MD led to more favorable changes in glycemic control and coronary risk factors, and delayed the need for drug therapy in overweight patients with newly diagnosed DM-2.

Another illustration of the importance of lifestyle.

MIGRAINE

A Problem Especially In Young Women With Aural Migraine Who Smoke And Use Oral Contraceptives

12-5 MIGRAINE WITH AURA AND INCREASED RISK OF ISCHEMIC STROKE

Roughly one quarter of people with migraine experience temporary neurological symptoms (aura) before onset of the headache. Aura is distinguished from other causes of brief recurrent neurological disturbance (e, TIA) by its gradual onset and disappearance, and its shorter duration.

Visual disturbances are the most common form of aura. Sensory and motor auras also occur. To identify patients with aura, it is necessary to detect only visual aura, since 99% of people with non -visual aura also have visual aura occasionally.

A recent study[1] clearly shows that the increased risk of ischemic stroke in patients with migraine is largely confined to those with aura. The risk of TIA and angina is also related to aura. Hemorrhagic stroke is not.

Patients with aura should be followed closely and treated aggressively for modifiable cardiovascular disease risk factors. But information to patients with aura should be put in context. The absolute risk of stroke is low, so a doubling of the risk is not cause for panic. At the population level, the risk deserves attention because the prevalence of migraines is so high.

The study also found the risk of ischemic stroke in patients with migraine is magnified by the combination of smoking and contraceptive use, mostly in women under age 45. Incidence of stroke is also increased in patients with frequent migraine.

Clinicians need to identify young women with aural migraine, particularly those who seek estrogen-containing contraception. Those without aura should not be denied the benefits of hormonal contraception.

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1 *See the full abstract*

An alert primary care clinician may be able to avert a tragedy.

"In particular, young women who have migraine with aura should be strongly advised to stop smoking, and methods of birth control other than oral contraceptives may be considered."

"Patients with migraine should be screened for traditional cardiovascular risk factors . . . and these risk factors should be modified."

The only patient with migraine with ischemic stroke I can recall encountering during my active practice career was a middle aged man.

OBESITY

"Offers A New Mode Of Action For The Treatment Of Obesity"

11-6 EFFECTS OF LIRAGLUTIDE IN THE TREATMENT OF OBESITY

Liraglutide is a glycogen-like peptide (**GLP**). It is 97% structurally analogous to native GLP, a gut-derived incretin hormone. Native GLP has a short elimination half-life (~ 1-2 minutes). Liraglutide has a half-life of about 13 hours. This allows once-a-day administration by subcutaneous injection. It was developed for treatment of type-2 diabetes.

Native GLP suppresses appetite and energy intake in both normal-weight and obese persons, as well as in patients with type-2 diabetes. There are several GLP receptors in brainstem nuclei, which are involved in appetite regulation.

This study assessed the effect of liraglutide on body weight (combined with low-fat diet and physical activity and counseling) on obese persons *without* diabetes.

Entered 564 men (n = 135) and women (n = 429) mean age 45, from 19 clinical research sites,

Body mass index of 30-40 (mean = 35) , stable body weight, and fasting plasma glucose less than 126 mg/dL. (Ie, none had known diabetes) None had major medical conditions. During the trial about 4% were diagnosed with type-2 diabetes; about 33% with prediabetes.

Randomly assigned to:

1) Liraglutide (1.2 mg; 1.8 mg; 2.4 mg; and 3.0 mg) s.c, once daily.

2) Placebo once daily s.c.

3) Orlistat 120 mg three times daily orally. (Open–label)

(I omitted data on the lower doses of liraglutide; the 3.0 mg dose was the most effective. RTJ)

All participants were instructed to adhere to a low-fat diet. (30% fat; 20% protein; 50% carbohydrate; about a 500 kcal / day deficit). They were encouraged to maintain or increase physical activity.

Outcomes:	Placebo (n = 98)	Liraglutide 3.0 mg(n = 93)	Orlistat (n = 95)
Completed trial (%)	79	82	79

Mean weight loss (kg)	-2.8	- 7.2	-4.4
Metabolic syndrome (%)			
Baseline	34	28	23
Week 20	21	11	20
Prediabetes (%)			
Baseline	36	31	29
Week 20	35	5	31
Safety data (Withdrawals %):			
Overall	19	12	17
With serous adverse events	1	1	0
Due to adverse events	3	5	3

Nausea and vomiting occurred within the first month in up to 33% of patients on 3.0 mg liraglutide Prevalence declined to about 10% at 5 months. Five withdrew because of nausea.

"Treatment with liraglutide, in addition to an energy-deficit diet and exercise program led to a sustained, clinically relevant, dose-dependent weight loss that was significantly greater than with placebo and orlistat."

Weight loss was accompanied by reductions in waist circumference, BP, and frequency of metabolic syndrome and prediabetes.

"Liraglutide was generally well tolerated. However, nausea and vomiting were more frequent than with other treatments, although these events were mostly transient and of mild or moderate intensity."

. "Liraglutide offers a new mode of action for the treatment of obesity, and improved efficacy compared with currently available therapies. Its effect on prediabetes suggests that it might be important for treating obese prediabetic individuals."

Conclusion: Liraglutide treatment over 20 weeks was well tolerated, induced weight loss, improved certain obesity-related risk factors, and reduced prediabetes.

I detected and was amused by the usual degree of "spin":

"Adverse events were generally mild and transient"

"Liraglutide was generally well tolerated"

(Primary care clinicians treat one patient at a time)

I wonder—Did the nausea and vomiting contribute to the weight loss?

The effect on prediabetes was encouraging.

I abstracted this article because GLPs may be an effective alternative to treatment of obesity.

OVARIAN CANCER

Ovarian Cancer Can No Longer Be Regarded As A Silent Killer.

9-5 DIAGNOSIS OF OVARIAN CANCER IN PRIMARY CARE

Ovarian cancer (**OC**) accounts for about 4% of all cancers in women. Overall 5-year survival is about 35%; stage I and II about 80-90%; stage III and IV about 25%.

Currently, only 30% are diagnosed in early stages.

There is no effective screening test. Presentation is usually to primary care.

This case-control study included women age over 40 between 2000-2007 in 39 primary care practices in England totaling over 66 000 patients aged 40-69, and 31 00 age 70 and over.

Identified 212 cases of OC (median age 67) by searching practice computer records. Five controls (n = 1060) were matched by age and practice. Studied symptoms occurring only in at least 5% of either cases or controls.

Seven clinical features remained in the final model:

	Cases n = 212 (%)	Controls n = 1066 (%)	Likelihood ratio
Abdominal distention	77 (36)	6 (0.6)	65
Loss of appetite	44 (21)	16 (1.5)	14
Postmenopausal bleeding	28 (13)	12 (1)	12
Abdominal bloating	35 (17)	21 (2)	8.4
Abdominal pain	112 (53)	92 (9)	6.2
Rectal bleeding	18 (8.5)	16 (1.5)	5.7
Urinary frequency	28 (14)	31 (2.9)	4.8
Physical signs:			
Abdominal mass	71(33)	1 (0,1)	360
Abdominal tenderness	51 (24)	19 (1.8)	14

"We calculated the risk of ovarian cancer across the whole range of important symptoms in the setting where diagnostic delays are most prevalent –primary care."

"We found seven symptoms . . . that were independently associated with ovarian cancer." Three of these symptoms –abdominal pain, abdominal distention, and urinary frequency—remained associated with OC when restricted to the period 6 months before diagnosis. (Ie, were present for longer than 6 months.)

Over half the women had a record of abdominal pain. It was equally common with early as

for advanced OC. It was present for many months before diagnosis in some women. The likelihood ratio of abdominal pain was low. This is a classical conundrum in those working in primary care—the low risk, but not zero risk symptom. (Ie, women would not generally be offered investigation on the basis of abdominal pain alone.)

Conclusion: Currently, the only realistic proposition for expediting the diagnosis of OC rests with its identification in women with symptoms. Symptoms are common and often reported even in early and potentially curable cancers. In particular, abdominal distention is a common important symptom and warrants investigation. Ovarian cancer is not silent.

PAIN

"Avoid NSAIDs , Consider Opioids"

7-5 NEW PAIN GUIDELINES FOR OLDER PATIENTS

Contradicting the guideline of 2002, an updated guideline issued by the American Geriatric Society (AGS) states that physicians treating patients aged 75 and older should avoid NSAIDs,

NSAIDs should be "considered rarely and with extreme caution in highly selected individuals". Despite improved understanding of risks of NSAIDs, including GI bleeding, they have remained a mainstay of pain therapy in the elderly. Physicians have shied away from opioids. "We feel that NSAIDs in many cases are more risky than many opioid strategies."

Physicians are advised to anticipate and monitor patients for adverse events associated with opioids, and to continually assess whether the therapy is meeting its goals. Breakthrough pain should be anticipated.

Opioids can induce delirium in older patients. This can be corrected by lowering the dose. Patients starting opioids can also experience anorexia, nausea, or vomiting. These adverse effects may dissipate over time. Constipation can be troublesome.

The guidelines advise against use of other classes of drugs: antidepressants including amitriptyline, imipramine, and doxepine. They cause a high risk of adverse events.

Treating pain in older adults requires an individualized approach. Physical interventions such as applications of heat and cold may help.

Acetaminophen remains the initial drug of choice. Caution against use in patients with liver disease.

The website www.americangeriatrics.org/education/pharm_management.shtml mentions:

Oxycodone

(eg, Percodan) 2.5-5 mg q 4 to 6 hours

Oxycontin	10 mg q 12 hours
Morphine	
Immediate release	2.5 to 10 mg q 4 hours
Sustained release	15 mg q 8 to 24 hours
Hydromorphone	
(Dilaudid)	1-2 mg q 3 to 4 hours
Transdermal Fentanyl	12-25 mg q 72 hours

This is a sea change. Use of opioids in the elderly calls for especial caution. Start with low doses. Monitor carefully. I believe many elderly will prefer NSAIDs because the adverse effects are less evident. Proton pump inhibitors will reduce the risk of GI bleeding. Primary care clinicians must watch for adverse effects of NSAIDs on BP, kidney function and heart failure.

I believe judicious use of opioids can offer greater pain relief than NSAIDs

On June 30, an advisory committee of the FDA recommended that the maximum daily dose of acetaminophen be lowered from 4000 mg to 2600 mg daily because of liver toxicity. (Individual tablets from 500 mg to 325 mg.)

McNeil company, makers of Tylenol, has strong objections. They believe that this will lead patients to switch to O-T-C NSAIDS, which are much more toxic.

Acetaminophen is a component of a host of preparations, both O-T-C and by prescription.
If these new recommendations are approved, the dose of acetaminophen in many preparations will have to be reduced.

PEPTIC ULCER

Effective for The Prevention Of Peptic Ulcers And Erosive Esophagitis

7-6 FAMOTIDINE FOR THE PREVENTION OF PEPTIC ULCERS AND OESOPHAGITIS IN PATIENTS TAKING LOW-DOSE ASPIRIN

There have been increasing reports of peptic ulceration, GI bleeding, and esophagitis in patients taking long-term low-dose aspirin (**LDA**).

This phase III randomized, double-blind, placebo-controlled trial compared efficacy of famotidine (a histamine -2 receptor antagonist; *Pepcid*; Merck; 20 mg twice daily) with placebo in 404 adult patients (mean age 63) for prevention of upper GI (**UGI**) complications of LDA.

All had been taking long-term LDA at baseline (for a mean of 3 years; the great majority taking 75 mg of aspirin daily). All continued to take LDA.

At baseline, 54% had mucosal scarring; 58% had mucosal erosions. (Subjects at this time had been taking LDA for a mean of 3 years.)

None had peptic ulcers or erosive esophagitis on endoscopy at baseline.

Outcome at 12 weeks:

Peptic ulcers of any size or erosive esophagitis or both	Famotidine + LDA	Placebo + LDA	Odds ratio
	5.4	32.5	0,12

Number needed to treat with famotidine to benefit (**NNTB**) one patient over 12 weeks = 32.5 – 5.4 = an absolute difference of 27% = NNTB = 3.7 patients treated for 12 weeks to prevent one lesion. (*My calculations RTJ*)

Four patients taking placebo developed upper GI hemorrhage vs 0 in the famotidine group.

Patients taking beta-blockers had a higher risk of GI complications. (24% vs 14%)

The majority of the participants in this trial had erosions or scars at baseline, indicating a high rate of upper GI lesions (including esophagitis) in persons taking LDA. They had a higher risk of UGI complications over 12 weeks.

I abstracted this article in part because famotidine is available at some pharmacies for $10 for 180 twenty mg tablets (3 months supply). Proton pump inhibitors are more expensive.

Cimetadine and ranitidine are also available for the same price. Famotidine has the longest plasma half-life and the longest duration of action.

In patients taking long-term LDA, upper GI lesions must occur almost universally over time. Lesions must come and go.

NSAIDs also frequently cause upper GI lesions. They are less likely to cause bleeding because, unlike aspirin, they have little effect on the clotting mechanism.

I did not understand why lesions were more frequent in patients taking beta-blockers.

Proton-pump inhibitors are routinely advised for prevention of UGI complications of LDA and NSAIDs. This is an example of newer (presumably more effective, but more expensive) drugs supplanting older drugs (PPIs vs H-2 blockers). Is this a demonstration of the power of the drug industry?

PHARYNGITIS

"The Potential Devastation Of Lemierre Syndrome Deserves Our Consideration."

12-8 EXPAND THE PHARYNGITIS PARADIGM FOR ADOLESCENTS AND YOUNG ADULTS

Recent evidence suggests that *Fusobacterium necrophorum* may cause as many as 10% of cases of pharyngitis in adolescents. *F necrophorum* can cause a severe complication of pharyngitis--Lemierre syndrome.

Lemierre described a clinical syndrome (1936) in adolescents whose illness started with tonsillitis. Although they improved initially, the adolescents developed clinical signs of bacteremia, including rigors, after about 4 days. They developed suppurative thrombophlebitis of the internal jugular vein and metastatic infections (most commonly pulmonary abscesses) due to *F. necrophorum* The mortality rate was high.

Lemierre syndrome remains life threatening. Patients may require intensive care, intubation and drainage of abscesses. Convalescence may be long.

Most patients present with pharyngitis several days before the Lemierre syndrome develops. Thus treating *F necrophorum* with appropriate antibiotics could prevent Lemierre syndrome.

It is estimated that *F necrophorum* causes about 10% of acute pharyngitis in adolescents. The risk of Lemierre syndrome after *Fnecrophorum* infection is likely higher than the risk of rheumatic fever after a streptococcus infection.

The diagnostic paradigm of pharyngitis in adolescents and young adults should include both group A beta-hemolytic streptococcal and *F necrophorum* pharyngitis. (The current paradigm supports teaching students to look for streptococcus [with a rapid test] and otherwise avoid antibiotics.)

The author suggests that, until we have better data, we should treat adolescents and young adults who present with at least 3 of the following for *F necrophorum*: 1) fever, 2) tonsillar exudates, 3) swollen tender anterior cervical adenopathy, and 4) lack of cough.

Macrolides (eg, erythromycin) are *not* effective against *F necrophorum.* Penicillin-metronidazole or clindamycin should be used.

Lemierre syndrome has been termed a "forgotten disease".

F necrophorum is a gram negative anaerobic non-spore forming bacterium well known to veterinarians. It is a common animal pathogen. It is a normal inhabitant of the human oropharynx.

Primary care clinicians should remember Lemierre syndrome. Early treatment may be life-saving.

Dr Robert Centor, the author of this article, proposed rapid clinical criteria for diagnosing group A streptococcal pharyngitis:

Fever

Tonsillar exudate

Tender anterior cervical adenopathy

Absence of cough.

The criteria must now include F necrophorum infection.

PHYSICAL ACTIVITY

Not Only Continuing PA, But Also Initiating PA, Was Associated With Better Survival And Function.

9-2 PHYSICAL ACTIVITY, FUNCTION, AND LONGEVITY AMONG THE VERY OLD

This study examined the influence of physical activity (**PA**) among an aging cohort during 18 years of follow-up. Is PA in older adults, including the oldest old (85+ years) associated with better survival, and functional and health benefits?

Followed a cohort of residents in Jerusalem born in 1920-21 from age 70 at baseline (in 1990) to 2008

Eight year mortality (%)		Physically active	Sedentary
Age 70		15	27
Age 78		26	41
Age 85	(3-year mortality)	7	24

Adjusted hazard ratio of mortality from any cause according to level of PA:

	< 4 h/w	> 4 h/w	Walking daily	Sports twice weekly
Age 70-78	1.00 (referent)	0.69	0.42	0.47
78-85	1.00	0.67	0.60	0.57
85-88	1.00	0.26	0.29	0.19

Changing levels of PA and survival: Not only continuing PA (consistent), but also starting PA at age 70+ (increasers) was associated with better survival compared with continuing sedentary participants and these who decreased PA (decreasers):

Mortality from ages (%)	Age 70 to 88	Age 85 to 88
Continuing PA (consistent)	32	8
Increased PA (increasers)	41	13
Decreased PA (decreasers)	56	25
Consistent sedentary	52	25

One important finding was the sustained protective effect of PA against functional decline. Physical activity level was associated with an independent functional status over time. Between

ages 78-85, independence in performing activities of daily living deteriorated less in those who were physically active (27% of those who were physically active lost independent function vs 42% of those who were not physically active.)

"Maintaining function is a central goal in aging, and awareness is increasing of the intimate relationship between the phenotype of frailty, loss of physiological reserves, and performance- based measures on functional decline as harbingers of preterminal trajectories of illness and mortality."

Among older people, PA may be instrumental in delaying the onset of the spiral of decline through its influence on a spectrum of pathways, which may include improved cardiovascular fitness, decelerated sarcopenia, reduced adiposity, and improved immunity.

Conclusion: Among the very old, not only continuing, but also initiating PA was associated with better survival and function.

I enjoy articles providing information on benefits of lifestyle interventions. They are the backbone of primary care medicine.

The authors comment on reverse causality (Those whose state of health is good at old age would be more likely to exercise.) They discount this possibility.

PNEUMONIA **(See COMMUNITY-ACQUIRED PNEUMONIA [9-1])**

RADIATION

"The Current Pattern of Medical Imaging is Exposing Many to Substantial Doses of Ionizing Radiation"

8-8 EXPOSURE TO LOW-DOSE IONIZING RADIATION FROM MEDICAL IMAGING PROCEDURES

Experimental and epidemiological evidence has linked exposure to low-dose ionizing radiation with the development of solid cancers and leukemia.

Persons at risk for repeated radiation exposure (workers in health care and the nuclear industry) are monitored and restricted to effective doses of 100 mSv[1] every 5 years—20 mSv per year) with a maximum of 50 mSv in any given year.

In patients undergoing medical imaging procedures, radiation exposure is typically not monitored, even though, in clinical practice, these procedures are frequently performed multiple times in the same patient.

This retrospective cohort study used claims data from a large health care organization (Over 26 million people [age 18-64] in 5 centers between 2005-2007.) Obtained estimates of effective radiation doses (assessed in millisieverts; mSv) from the published literature.

Identified over 950 000 subjects, mean age 36. Identified a total of 3,442,111 imaging procedures associated with radiation exposure in 655,613 (69%) subjects over the 3 years—a mean of 1.2 procedures per person per year. The mean effective dose was 2.4 mSv per person year. The median effective dose was 0.1 mSv per person year. (This indicates that many outliers received large radiation doses.)

Moderate doses (3-20 mSv /y) were incurred at an annual rate of 194 per 1000 enrollees; high doses (>20-50 mSv/y) at an annual rate of 19% per 1000; and very high doses (> 50 mSv) at an annual rate of 2 per 1000. Many procedures were performed on multiple occasions on the same patient.

Exposure is of greatest concern in younger patients (age 18-43) 50% of whom received at least one procedure. Rates for high and very high exposure were not trivial in younger patients. More than 30% of men and 40% of women under age 50 received doses exceeding 20 mSv.

Related risks accrue over a lifetime. Cancer may be more likely to develop in women than in men after similar levels of exposure.

Conclusion: The current pattern of use of medical imaging in the US among non-elderly patients is exposing many to substantial doses of ionizing radiation.

This is another good example of the need for co-ordinated care as in a primary –care medical home. Someone must list and add all radiation exposures.

Primary-care clinicians must ask themselves: Is this imaging test really necessary? Will it benefit more than harm? Will it change my treatment or advice?

See the full abstract for a list of the average effective dose(in mSv) delivered by various imaging procedures.

1 I am woefully ignorant about radiation physics. Although primary care clinicians do not need to understand the basics, they should understand the potential danger of multiple exposures from radiation.

I attempted a computer search to learn more. For what it is worth:

A gray (symbol Gy; in honor of Louis H Gray, a British physicist) is the SI unit of absorbed radiation dose due to ionizing radiation. It is the absorption of 1 joule of energy in the form of ionizing radiation by 1 kg of matter. It measures the deposited energy of radiation.

A sievert (symbol Sv; in honor of Rolf Sievert, a Swedish medical physicist) is also a SI unit. It attempts to reflect the biological effects of radiation (as opposed to the physical). It has the same dimensions as the gray—joules per kilogram. The equivalent dose to a tissue is found by multiplying the absorbed dose (in gray) by a quality factor

dependent on radiation type, part of the body irradiated, the time and volume over which the dose is spread, and even the species of the subject.

An older unit of the equivalent dose is the rem (Roentgen equivalent man). In some countries, rem and mrem continue to be used along with Sv and mSv, causing confusion.

RENIN-ANGIOTENSIN SYSTEM (See DIABETES [7-8]

SALT

Aim for 5 Grams of NaCl Daily, or Less

12-1 THE CASE FOR POPULATION-WIDE SALT REDUCTION GETS STRONGER

Excess intake of sodium chloride has an important and probably predominant role in the pathogenesis of raised BP. On average, as salt intake increases, BP increases. The importance of this association cannot be overstated. The evidence is indisputable.

Several studies have estimated the societal benefits of population-wide salt reduction. One study estimated that across 23 countries with a high burden of chronic disease, 850 000 lives would be saved each year from a reduction in salt intake to 5 grams daily. This is the recommended limit set by the WHO.

A recent analysis reported that an average daily intake of 5.8 gram NaCl (2300 g sodium; the recommended upper limit in the US) would reduce the prevalence of hypertension by 11 million, save $18 billion in health care costs, and gain 312 000 quality adjusted life years. This line of reasoning, however, is indirect.

A meta-analysis in this issue of BMJ is a welcome addition to the medical literature.

The meta-analysis included 13 cohort studies and 19 independent samples, which demonstrated a higher salt intake is associated with increased incidence of stroke. A 5 gram increase in salt intake was associated with a 23% higher risk of stroke. And a 17% higher risk of CVD.

Of course, this is nothing new. I abstracted the article because I believe salt is the neglected aspect of the healthy diet. Few individuals calculate their salt intake. They pay less attention to salt than to fats and calories.

Additionally, those of us who eat commercially prepared foods face difficulties in reducing salt intake. Ideally, to reduce salt intake food must be prepared at home. And the salt shaker removed from the table.

SLEEP

"A Public Health Problem"

12-9 PERCEIVED INSUFFICIENT REST OR SLEEP AMONG ADULTS: United States, 2008

The importance of chronic sleep insufficiency is under-recognized as a public health problem. It is associated with numerous physical and mental health problems: injury, loss of productivity, and mortality.

About 29% of US adults report sleeping less than 7 hours per night. Millions have chronic sleep and wakefulness problems.

This report summarizes the results of a survey of 50 states and 3 territories in 2008. Among 403 981 respondents, 31% had no difficulty sleeping (reported no days of insufficient sleep or rest during the preceding 30 days), 41% reported 1 to 13 days of insufficient sleep, 17% reported 14-29 days, and 11% reported insufficient rest or sleep every day during the preceding 30 days

Health care providers should consider adding an assessment of chronic rest or sleep insufficiency to routine office visits so they can make needed interventions or referrals to sleep specialists.

According to the National Sleep Foundation, adults need 7 to 9 hours of sleep each night. Primary care clinicians should evaluate patients who report chronic insufficient sleep and advise them of effective behavioral strategies including keeping a regular sleep schedule, and avoiding stimulating activities within 2 hours of bedtime.

"Pharmacological intervention also might be warranted."

Primary care clinicians are very well aware of how common sleep problems are. I would guess that the major response to a complaint about sleep would be to reach for the prescription pad.

Is this the best response? Would not a try at improving sleep hygiene be the best first step?

I have had no experience with sleep specialists. They might help a minority of patients, but the burden remains on primary care.

Information about sleep hygiene and a print-out to give patients can be obtained at:

www.sleepfoundation.org/article/ask-the-expert/sleep-hygiene

SMOKING

"If At First You Don't Succeed . . . "

11-7 THE IMPACT OF REPEATED CYCLES OF PHARMACOTHERAPY ON SMOKING CESSATION

This study tested the impact of repeated courses of pharmacotherapy to help smokers recover from relapses and engage in new cessation efforts. It followed a cohort of smokers offered up to 4 courses of pharmacotherapy over 2 years.

Recruited smokers (n = 726), regardless of their interest in quitting, from 50 rural primary care clinics in Kansas. All were over age 18 and had smoked over 10 cigarettes daily.

At months 0. 6, 12, and 18, participants were asked if they wanted to receive a 6-week course of 21 g/d nicotine patch, or a 7-week course of buproprion sustained-release 150 mg twice daily.

Defined cessation as a self-reported 7-day abstinence at the end of each 6-month cycle.

Cessation rates were consistently higher for users of pharmacotherapy compared with nonusers.

Association between multiple consecutive cycles and cessation rates:

	720 smokers	
First cycle	464 requested medications (64%)	262 did not request meds (36%)
	81 quit (17%)	20 quit (8%)
Second cycle	202 requested medications (53%)	
	25 quit (12%)	
Third cycle	81 requested medications (46%)	
	13 quit (16%)	
Fourth cycle	44 requested meds (65%)	
	7 quit (16%)	

(Total of 27% [126 of 464] quit vs 8% of untreated group)

Many smokers persisted in requesting drugs for up to 4 cycles. Between 12% and 17% quit at each cycle. (The probability of quitting was not related to the number of previous drug-assisted attempts.)

One of 2 smokers was willing to make a second drug-assisted attempt within 6 months of a treatment failure. Willingness to reengage in treatment did not diminish over time.

“These results support a model of care in which smokers in whom treatment initially fails are quickly reengaged in a new pharmacotherapy-assisted quit attempts.”

The goal is permanent abstinence,

This study defined abstinence as cessation for only 7 days.

Nevertheless, I believe some patients will indeed stop permanently after one or more attempts to quit. Some, of course, will relapse. By my calculation, in this study, the NNT to achieve one cessation for 7 days = 5

This is a possible practical application for primary care practice. Some clinicians and patients will be willing to try again and again. And after several attempts, some will succeed.

Subjects in the study were-selected regardless of their interest in cessation. This makes the study more generalisable.

Would not a primary-care clinician's success in getting one person to quit be equivalent to one coronary bypass operation?

Six of Every 100 Primary Care-Based Smokers Could Achieve Abstinence

12-6 COMPARATIVE EFFECTS OF 5 SMOKING CESSATION PHARMACOTHERAPIES IN PRIMARY CARE CLINICS

Primary care is the ideal environment in which to study comparative effectiveness of cessation treatments:

1) Many smokers report being receptive to advice from their primary care provider (**PCP**).
2) More than 70% of smokers visit their PCP annually.
3) Health considerations are especially salient in a clinical setting, making patient visits "teachable moments".
4) A majority of smokers express interest in cessation treatment. Many prefer more intensive treatment.
5) Primary care based cessation treatments are cost effective.

The Public Health Service guidelines recommend brief counseling and cessation medication for smokers. This will increase likelihood of successful quitting.

This study recruited over 1300 smokers in primary care clinics. All were motivated to quit. Mean age = 44; age at first cigarette 14; cigarettes smoked per day 20; previous quit attempts 6

Randomized to 5 different pharmacotherapies (provided free of charge), in combination with telephone counseling provided through a state sponsored tobacco quit line. Participants were informed which drug(s) they were to receive.

The 5 pharmacotherapies (all drugs FDA approved): 1) Nicotine patch; 2) Nicotine lozenges 3) Bupropion SR; 4) Bupropion SR + nicotine lozenge; 5) Bupropion SR + nicotine patch.

Cessation counseling was provided by telephone, the Wisconsin Tobacco Quit Line.

Among 7100 eligible smokers attending routine primary care medicine, 1300 (19%) enrolled in the study.

Sixty % of those enrolled did not use telephone counseling.

Participants who used fewer than 90 minutes of counseling had an abstinence rate of 20%

(almost equal to that of non-users of counseling). Those that had more than 90 minutes of counseling time had an abstinence rate of 36%.

Abstinence rates at 6 months:	%
1) Nicotine patch	18
2) Nicotine lozenge	20
3) Bupropion SR	17
4) Bupropion SR + patch.	27
5) Bupropion SR + lozenge	30

The buproprion + lozenge combination was especially effective relative to the monotherapies, with approximately a doubling of abstinence rates at 6 months.

About 1 in 5 primary care smokers attending primary care are willing to undertake an unplanned quit attempt during a primary care visit that included the opportunity to receive free medication and telephone counseling.

"Assuming that 1 in 5 smokers visiting a primary care clinic for routine care will undertake an unplanned quit attempt and that up to 30 in every 100 of these smokers making a quit attempt could achieve long-term (6 month) cessation, the overall success (defined as long-term abstinence) of this intervention model corresponds to 6 of every 100 primary care-based smokers (ie, all smokers including those who are not motivated to make a quit attempt) achieving long-term abstinence."

Conclusion: Provision of free cessation medications plus quit line counseling arranged in the primary care setting holds promise for assisting large numbers of smokers to quit.

The trial concluded that counseling + drugs, not drugs alone, was essential to achieve abstinence.

Some of these smokers must have relapsed after the trial concluded. Try, try again.

Achieving a success rate of 6% is a major public health achievement.

SORE THROAT **(See also PHARYNGITIS [ ])**

"A Single Dose Of Corticosteroids May Be Sufficient."

8-3 CORTICOSTEROIDS FOR PAIN RELIEF IN SORE THROAT: *Systematic Review and Meta-Analysis*

Corticosteroids inhibit transcription of pro-inflammatory mediators, which cause inflammation and pain. They are beneficial in other respiratory tract infections such as acute sinusitis, croup, and infectious mononucleosis.

This systematic review evaluated whether corticosteroids improve symptoms of sore throat.

A literature search included 8 randomized controlled trials of 743 patients (half children; half adults) comparing systemic corticosteroids with placebo in outpatient settings. All had clinical signs of acute tonsillitis, pharyngitis, or a clinical syndrome of "sore throat".

In a pooled analysis of 4 trials, patients treated with corticosteroids were three times more likely to have complete remission of pain at 24 hours, Number needed to treat to benefit one patient = 4.

In 3 trials, corticosteroids increased likelihood of complete resolution of pain at 48 hours. Number needed to treat = 3.

In patients with exudative sore throat, corticosteroids reduced the mean time to onset of pain relief (mean difference = 6 hours). All 3 categories of sore throat (exudative, bacterial, and severe) had reduced time to onset of pain relief.

Time to onset of pain relief was similar when oral or intramuscular corticosteroids were used.

Corticosteroids significantly increased the proportion of patients with sore throat who experienced complete relief of pain at both 24 and 48 hours. Fewer than 4 patients needed to be treated with corticosteroids to prevent one patient from continuing to experience pain at 24 hours.

All effects were in addition to antibiotic therapy.

"The effects of corticosteroids on resolution of pain were most apparent in the initial 24 hours, which implies that a single does of corticosteroids may be sufficient."

Conclusion: Corticosteroids (given in addition to antibiotics) provided symptomatic relief of pain of sore throat, mainly in participants with severe exudative sore throat.

Corticosteroid use in sore throat should be individualized—limited to those with greatest distress. And only for one or two days. I believe they may offer considerable relief to select patients. Although adverse effects would be rare, they are still possible, even with short duration use. The next question—should corticosteroids ever be used alone, without antibiotics?

STATIN DRUGS

Risk Reduction In All Cause Mortality Of 12% and Major Coronary Events Of 30%, over 4 years

7-3 THE BENEFITS OF STATINS IN PEOPLE WITHOUT ESTABLISHED CARDIO-VASCULAR DISEASE BUT WITH CARDIOVASCULAR RISK FACTORS

This meta-analysis of randomized trials investigated whether statins reduce all-cause mortality and incidence of major coronary and cerebrovascular events in people without established CVD, but with risk factors.

Included 10 randomized trials of statins (n = over 70 000 persons; 33% women; 23% with

diabetes; mean age 63) compared with controls (placebo, active control, or usual care). Reported mortality and CVD events as primary outcomes. .

Mean follow-up = 4 years.

The dose and type of statin varied.

Risk factors included: age over 65, diabetes, smoking, increased BMI, elevated LDL-cholesterol.

All-cause mortality:

Controls: 1925 of 33 793 (5.7%)

Statin group: 1725 of 33 683 (5.1%)

(Odds ratio = 0.88; 12 % reduction; NNTB for 4 years to prevent one death = 166)

Major coronary events:

Controls: 1266 of 23 946 (5.4%)

Statins: 966 of 23 823 (4.1%)

(Odds ratio – 0.70; 30% risk reduction; NNTB for 4 years to prevent one event = 76)

Major cerebrovascular events:

Controls: 2.3%

Statin group: 1.9%

(Odds ratio = 0.81, 19% reduction; NNTB for 4 years to prevent one event = 250)

No significant treatment heterogeneity was found between the sexes, between the elderly and young people, and between people with and without diabetes.

"Given the favorable effect of long-term statin treatment, it would be wrong to deny these benefits to people at increased risk for cardiovascular disease."

Although the NNTB (number needed to treat to benefit one patient) is high, on a population basis, the benefit would be great..

Given that age itself is a major risk factor and other risk factors are ubiquitous, would this not lead to near universal statin use?

The benefits of statins would be much lower in younger persons without risk factors and in those with few risk factors. Use of statins for these persons would be more problematic. It would depend on a calculation of the risk and the patient's choice after being fully informed. There are risks and costs of statin therapy. In some patients the benefit / harm-cost ratio may be low.

STROKE (See Migraine [12-5])

TROPONIN ASSAYS

A Clinical Diagnosis of MI Depends Both on Elevated Levels of Troponin and on Clinical Data

8-7 CLINICAL APPLICATION OF SENSITIVE TROPONIN ASSAYS

Now, more sensitive troponin assays (**STA**) have become available. They are widely used. Some practitioners are not certain about the cutoff values for clinical interpretation.

Clinical evidence conclusively shows that STA offers levels of sensitivity and specificity for cardiomyocyte injury superior to creatine kinase-MB. (CK-MB exists in tissues other than the myocardium.)

For the older original troponin, a cutoff value was based on the distribution of values in healthy reference populations. It defined the upper normal at the 97.5^{th} or 99^{th} percentile of a reference population. This value is used for many clinical laboratory tests. For troponin, professional societies recommended the 99^{th} percentile as more conservative than the 97.5^{th} percentile. Since 2000, the guidelines have endorsed a single cutoff value for the diagnosis of MI at the 99^{th} percentile.

As a result of better precision, the new assays can detect substantially lower concentrations of troponin. This has led to two critical questions:

1) What is the diagnostic sensitivity of the more sensitive assays?

2) Is a low concentration of detectable troponin clinically meaningful?

For diagnostic performance, accuracy for the diagnosis of MI was improved with the sensitive assays (94 to 96%) as compared with the older assays (85 to 90%).

The accuracy of the sensitive assays within 3 hours after onset of pain was 92 to 94%, as compared with 76% for the old standard assay.

However, the improved sensitivity (more true positives) was accompanied by a reduced specificity (more false positives) for MI, as compared with the standard assay. Consequently, for every 100 patients with an elevated troponin detected by the sensitive test, only 77 had a final diagnosis of MI.

Two studies showed that the new generation of sensitive assays for troponin improved overall diagnostic accuracy. The results also confirm a trade-off of superior clinical sensitivity (more true positive tests) for diminished clinical specificity (more false positive tests) for the diagnosis of MI.

This does not impugn the tissue specificity of troponin, rather it underscores that myocardial injury may result from a variety of mechanisms. It also shows that a clinical diagnosis of MI depends both on elevated levels of troponin and on clinical data (ie, the presence of typical symptoms that support ischemia as the cause). It is not possible to reliably discriminate ischemia from non-ischemic cause (eg, myocarditis) by simply raising the cutoff value.

At least 6 studies have firmly established the prognostic relevance of small elevations of STA.

Collectively these data indicate a doubling of the adjusted risk of death or recurrent ischemia in patients with a small troponin elevation.

Among patients with a high probability of acute coronary syndrome, the approximately 20% of patients who were missed with the use of outdated cutoff values for troponin were at high risk for recurrent events.

"Sensitive assays for troponin are a step forward with respect to overall diagnostic accuracy for myocardial infarction".

VENOUS THROMBOEMBOLISM

D-Dimer Tests Can Rule Out DVT, Not Rule It In

8-6 DIAGNOSIS OF VENOUS THROMBOEMBOLISM

The signs and symptoms of venous thromboembolism (**VTE**) are common, but non-specific. Both over-diagnosis and under-diagnosis are associated with substantial morbidity and mortality.

D-dimers are fibrin degradation products resulting from endogenous fibrinolysis associated with intravascular thrombosis. A non-specific increase in D-dimer concentrations is seen in many situations, precluding its use *for diagnosing* VTE. (Ie, low specificity for VTE—many false positive tests.) However, a low D-dimer concentration is thought to *rule out* presence of circulating fibrin, and therefore rule out VTE.

No test reliably rules out VTE without taking into account the clinical probability of the disease. ("The clinician's estimate of the *pretest* probability of a target disorder is a crucial determinant of the direction and extent of the diagnostic work-up.")

Point–of-care D-dimer tests are particularly useful for doctors who need rapid information.

A key point is how doctors apply Bayesian reasoning in day-to-day clinical practice. The authors used Bayes' theorem to calculate the *posttest* probability of VTE, conditioned by the likelihood ratio as a function of the *pretest* probability. They assumed a pretest threshold probability of 2% VTE, below which further testing was not warranted. Pretest probability had to be below 8-10% to rule out VTE with confidence when point-of-care D-dimer testing was negative.

The authors present 4 new point-of-care D-dimer tests. One of the best is the "Cardiac D-dimer" test.

Negative predictive value of the point-of-care "Cardiac D-dimer" test for VTE:

Pretest likelihood of VTE	Post test probability of VTE given a negative test result
Low risk (5%)	0.4 (Ie, very unlikely to be VTE)

The abstract also presents some guidance about judgment of pretest probability of pulmonary embolism and deep venous thrombosis.

VITAMIN D

Reduces Risk Of Falls In The Elderly By 20%. Use At Least 1000 IU Daily.

10-6 FALL PREVENTION WITH SUPPLEMENTAL AND ACTIVE FORMS OF VITAMIN D: A Meta-Analysis

Vitamin D (**D**) has direct effects on muscle strength, modulated by specific D receptors in muscle. Several trials, of older individuals at risk of D deficiency, reported that supplementation improved strength, function, and balance in a dose-related fashion. This translated into a reduction in risk of falls.

This meta-analysis assessed the efficiency of D supplementation, with and without calcium, for preventions of falls

A systematic search 1995-2008 included 8 randomized trials (n = 2426; 81% women; approximate mean age = 80). All studies were double blind. All subjects were age 65 and older and in stable health living in the community. All received a defined oral dose of: 1) supplemental vitamin D2 (ergocalciferol; 3 studies), or D3 (cholecalciferol; 5 studies), or 2) an active form of vitamin D (1alpha-hydroxy-claciferol or 1,25 dihydroxy-chole-calciferol).

Outcomes analyzed on an intention –to-treat basis. Treatment duration varied from 2 months to 3 years.

Trials assessing D supplements:

- The daily dose ranged from 200 IU to 1000 IU.
- The pooled relative risk (**RR**) of a fall in studies with 700-1000 IU was 81%. (A reduction of 19%.)
- The RR of falls in those receiving a dose less than 700 IU/d was 1.10.
- Achieving a serum 25(OH)D concentration of 24 ng/mL (60 nmol/L) or more resulted in RR of falls of 0.77 (23% reduction). Concentrations of less than 24 ng/mL (60 nmol/L) had no effect on reduction of number of falls.

Trials of oral active forms of D:

- Subjects were more likely to experience hypercalcemia than those in the control group.
- The pooled RR of fall was 0.77 (Risk reduction = 23%)
- No additional benefit compared with supplements.

No fall reduction was seen in subjects receiving a dose of less than 700 IU or serum concentrations less than 24 ng/mL (60 nmol/L). Benefit was noted as soon as 2 to 5 months of treatment.

Fall prevention may not depend on calcium supplementation.

"Active forms cost more and have a higher risk profile, so we believe adequate dosing of supplemental vitamin D should be preferred."

The renaissance of vitamin D has been fascinating. It is no longer merely for prevention of rickets. It is not really a vitamin.

Benefits in mortality and at least 10 diseases and conditions have been attributed to supplemental D. There have been claims that D improves immune function.

Where do we now stand?

D is a steroid-like hormone derived from dehydro-cholesterol, rather than a vitamin. It has effects on many cells in the body.

Deficiency is widespread, especially in northern latitudes and among the elderly who are not exposed to sunlight. The cutpoint for normal serum levels is not yet established. It is usually cited as 15 to 30 ng/mL. Serum assays are expensive. Some are inaccurate.

D does improve bone strength and lowers risk of fractures in the elderly (along with calcium Supplements).

The benefit / harm-cost ratio of supplemental D is very high. D is not harmless, especially from high doses. Hypercalcemia, hyperphosphatemia and kidney stones may occur. Toxicity from 1000 IU daily is likely to be very low. Years of observations may be required to establish harms and the dose.

Most studies have been observational or epidemiological. They are subject to bias and confounding. Many disagree. It will take years to firmly establish the true benefits. Randomized, placebo-controlled trials are not ethical. Trials would not be supported by drug companies because D is so inexpensive. There would be no profit motive.

We now treat all individuals routinely and empirically at daily doses recommended by the Institute of Medicine in 1997. The recommended daily supplemental dose has been too low. It may be safe and advisable to increase the recommended daily dose to 1000 IU. Vitamin D3 (cholecalciferol) is more effective than D2 (ergocalciferol).

Some elderly patients would benefit from empiric treatment with 1000 IU daily .

But, sound evidence of efficacy and effectiveness is limited. What is deficiency? What is insufficiency?

12-4 MORE EVIDENCE ON LOW VITAMIN D LEVELS

Many studies report that D deficiency and insufficiency are tied to poor health outcomes from a variety of conditions in a large proportion of the U.S, population. Conditions cited include osteoporosis and bone fracture, muscle weakness, cancer, respiratory tract illnesses, auto-immune disease, diabetes, schizophrenia, depression, lung dysfunction, kidney disease, and cardiovascular disease.

The studies are mainly retrospective. This makes it difficult for regulatory bodies or specialty societies to develop specific recommendations for raising levels for minimum D intake. And leaves some physicians reluctant to aggressively diagnose and treat patients for deficiency.

The National Health and Nutrition Examination Survey (2001-2004) found that, among over 9700 children and young adults, 9% had deficiency in 25-OH-D (<15 ng/mL), and 61% had insufficiency (15-29 ng/mL).

"Vitamin D used to be all about rickets, and whatever the level you needed to prevent rickets was the accepted level. But as other risk factors have arisen, the recommended level should also be on the rise."

Other observers have cautioned that most of the evidence is epidemiological, in which D levels have been associated with various disease processes. This does not establish cause and effect. Randomized, controlled trials are needed.

The Institute of Medicine is scheduled to report regarding D intake in May 2010. It is expected that it will emphasize an increased intake of D and encourage its further use as a food additive. The IOM will look beyond bone health to consider other chronic diseases. Currently the IOM recommends that the upper intake should be limited to 1000 IU for infants up to age 1 and 2000 daily for all over age 1.

The benefit / harm -cost ratio of D is very high. Benefits seem to be high (although not likely as widespread as some have predicted); harms low; and costs very low (Three cents for 1000 IU in some pharmacies.)

Many primary care clinicians adhere to the traditional approach--testing for deficiency, and then prescribing. Most individuals in the U.S. do not consult physicians frequently, and when consulting, D levels may not be considered.

I believe the "polypill" principle would apply to D--ie, recommending almost universal use without pretesting and without follow-up.