PRACTICAL POINTERS

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PRIMARY CARE MEDICINE

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INDEX and SYNOPSIS

JANUARY-JUNE 2011

PRACTICAL CLINICAL POINTS

MEDICAL SUBJECT HEADINGS

HIGHLIGHTS AND *EDITORIAL COMMENTS*

LINKS TO FULL ABSTRACTS

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This index-synopsis is a reference document based on articles abstracted from 6 flagship journals July - December 2010. It provides a means of reviewing and recalling to memory, in an evening or two, practical clinical points of importance to primary care.

The numbers in the brackets refer to the abstract. For example, [1-6] refers to the sixth article abstracted in January.

It consists of 3 parts:

1) "Practical Clinical Points": This provides an instant reminder of points of clinical interest and importance, which primary care clinicians may wish to advise patients about, consider, and be aware of. Some points are new; some emphasize older points.
2) "Medical Subject Headings" (MeSH): A list of medical subject headings from ADOLESCENT BMI to VITAMIN arranged alphabetically
3) "Highlights of Abstracts and *Editorial Comments*": 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) Links fo full abstract: The full abstracts may be accessed from the monthly issues on the website. They provide more detailed information, and the citation.

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

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

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

PRACTICAL CLINICAL POINTS

JANUARY – JUNE 2011

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

[1-1] The Institute of Medicine has raised the RDA for vitamin D to 600 IU daily. There is a paucity of randomized clinical trials regarding vitamin D in prevention of numerous diseases. Other than the benefit on bone health, these associations are best described as hypotheses of emerging interest.

[1-2] Serum 25-hydroxy vitamin D (D; 25-OHD) *deficiency* (below 10 ng/mL; 25 mmol/L), has long been recognized as a medical condition. It is characterized by muscle weakness, bone pain and fragility fractures. Vitamin D *insufficiency*, variously described as 25-OHD 10 to 20, or 10 to 29 ng/mL without overt clinical symptoms, has recently become a concern. The average dietary intake of D (including supplements) in the US is 200 IU per day. Skin-derived synthesis of D is quite variable.

[1-3] Proteinuria, as well as e-GFR, is a risk factor for progression to end-stage kidney disease. Even a small amount should raise a red flag.

[1-4] The poorly absorbed antibiotic, rifaximin, is reported to benefit *non-constipation* irritable bowel syndrome.

[1-5] Long-term low-dose daily aspirin is reported to reduce risk of colon cancer and other cancers. Adverse effects of aspirin are a draw-back.

[1-6] Herpes zoster vaccine is effective in older adults.

[2-1] In patients with systolic hypertension, introduction of automated BP measurement in the office, compared with usual manual BP determinations, reduced the white-coat response.

[2-2] Light to moderate alcohol consumption was related to reductions in multiple cardiovascular outcomes, including coronary heart disease, stroke, and all-cause mortality.

[2-3] Light to moderate alcohol consumption was related to improve levels of several biologic markers for coronary heart disease. These include increased HDL-cholesterol and decreased fibrinogen. There was no difference related to the types of alcohol.

[2-5] Remember the caregivers, especially those who care for family members with long-term disabilities and dementia. Caregivers need care and support too.

[2-6] The hypothesis that C-reactive protein modifies the vascular benefits of statin drugs is *not* supported.

[3-1] In addition to vascular disease, diabetes is associated with premature death from several cancers, infectious diseases, self-harm, and degenerative disorders.

[3-2] In patients without "hypertension" (ie, with "prehypertension") lowering the systolic BP was associated with decreased risk of stroke, congestive heart failure, and all-cause mortality.

[3-3] Surrogates for patients at end-of-life who lack decision-making capacity, take comfort when they know they are following the wishes of the patient. The responsibility of decision-making stresses surrogates. Physicians may help to relieve the stress.

[3-4] A complex review of multiple drugs concludes that fluoxetine is preferred to treat generalized anxiety disorder.

[3-5] The American Diabetes Society supports glucagons-like peptide analogues as an alternative third-line treatment for overweight and obese patients with diabetes.

[3-6] The Institute of Medicine concludes, despite biological plausibility and widespread enthusiasm, the evidence that vitamin D reduces risk of cancers is inconsistent and inconclusive.

[4-1] Prevention of coronary heart disease (CHD) should begin at an early age. BMI in adolescence was an independent predictor of CHD in adulthood even when it was well within what is now defined as in the normal range. Incident diabetes was mainly due to high BMI in adulthood..

[4-2] "There are few healthcare interventions more impactful than helping smokers quit. " This article outlines physician advice and drug treatment approaches to cessation.

[4-3] This excellent review article outlines the British approach to hypertension—first-line drugs are 1) angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. Followed by calcium blockers and diuretics. Beta-blockers have fallen out of favor. Patients with low rennin levels (older patients) respond well to calcium blockers and diuretics..

[4-4] Promoting shared decision-making is increasingly seen as something that is needed to keep pace with changing social expectations. “Nothing about me without me.” The ability to share decision making must be seen as a component of what it means to be a health professional.

[4-5] The Salzburg Statement on Shared Decision-making. In2010 representatives from 18 countries met in Salzburg and agreed on a statement that patients can and should play in health care decisions.

[4-6] In older patients with diabetes, tight control often leads to substantial burdens (dietary restrictions, insulin reactions, and hypoglycemia). Goals for treatment of the elderly should focus on quality-of-life and symptom management.

[5-1] Clinical research is typically performed to address questions of: 1) Efficacy: can the intervention work under ideal settings? 2) Effectiveness: Does it work when generalized to the real world and applied to individual patients? 3) Cost effectiveness: Is it worth it, and should it be paid for? Relying on efficacy data to draw conclusions about effectiveness is an important source of clinical uncertainty.

[5-2] Medical treatment of TIA and minor stroke: 1) Acute—immediately start antiplatelet therapy, preferably with aspirin- dipyridamole. 2) Long term secondary treatment—continue antiplatelet therapy (warfarin is not recommended), control lipids and BP. Treatment of stroke secondary to atrial fibrillation differs.

[5-3] A purified form of hemoglobin A1C has been prepared. This will change reporting from % to mmol HbA1c/mol hemoglobin.

[5-4] The FDA has approved the direct thrombin inhibitor dabigatran for treatment of non-valvular atrial fibrillation

[5-5] Middle-aged women who develop atrial fibrillation are at increased risk of death. Anticoagulation is essential, along with efforts to decrease CVD risk factors

[5-6 New European guidelines on atrial fibrillation. Key changes include identification of more people at risk of embolic stroke, wider use of oral anticoagulants, a more pragmatic approach to rate control, and lower threshold for catheter ablation.

[6-1] A new guideline covers ways to prevent and treat hypertension in elderly people. It was based on a study of over 3000 hypertensive patients 85 years of age and older who were randomized to receive a diuretic alone or an added ACE inhibitor if needed to reach a target of 150 systolic. Systolic was reduced by a mean of 15 mmHg. Compared with placebo, over 2 years, the death from CVD causes and all-cause mortality were reduced by 20%.

[6-2] Determination of BP in the office is often done without due care. Suggestions for improvement

[6-3] Every 2-hours of TV viewing per day was linearly associated with increased risk of type-2 diabetes, CVD mortality, and all-cause mortality.

[6-4] Update on the "polypill". The concept refuses to die. The role of aspirin is downgraded. Almost all benefits were due to reductions in BP and improvements in lipids

[6-5] The aromatase inhibitor exemestane reduced risk of primary breast cancer in a high-risk group. At a cost of $1 405 922 to prevent one case.

[6-6] Is X-ray scanning in airports safe? The radiation dose of a full-body scan is truly trivial.

MEDICAL SUBJECT HEADINGS (MeSH)

JANUARY – JUNE 2011

ADOLESCENT BMI (Se OBESITY [2-4])
AIRPORT FULL BODY SCANS
ALCOHOL
ANGIOTENSIN CONVERTING ENZYME INHIBITORS (See HYPERTENSION [3-2)])
ANGIOTENSIN RECEPTOR BLOCKER (See HYPERTENSION [3-2)]
ANTICOAGULANT THERAPY (See DABIGATRAN [5-4]
ANTI HYPERTENSION TREATMENT (See HYPERTENSION [3-2)]
ANXIETY DISORDER
ASPIRIN
ATRIAL FIBRILLATION

BREAST CANCER

CARDIOVASCULAR DISEASE (See ASPIRIN [2-2] [2-3]; POLYPILL 6-4])
CARE GIVING
CANCER (See ASPIRIN 1-5;)
C--REACTIVE PROTEIN

DABIGATRAN
DECISION MAKING
DIABETES
(See also TELEVISION VIEWING)
DYING

EFFICACY AND EFFECTIVENESS

GLUCAGONS-LIKE PEPTIDE (See DIABETES [3-5])

HIGHLIGHTS AND *EDITORIAL COMMENTS*
JANUARY- JUNE 2011

AIRPORT FULL BODY SCANS

"No Significant Threat Of Radiation From The Scan"

6-6 AIRPORT FULL BODY SCANNING: What is the Risk?

The Transportation Security Agency (TSA) has deployed 486 full body scanners (FBS) in airports in the US. More are on the way.

There are two types of FBS. Each generates a detailed outline of the human body:

The millimeter-wave scan emits extremely low-energy waves—each scan delivers a small fraction of the energy of a cell phone. The scan captures reflected energy.

The backscatter scanning machine (the most commonly used type) uses very low doses of X-rays. Scans used in medical imaging transmit energy *through* the body and deposit it *in* the body. Backscatter scanners detect radiation that *reflects off* the person's body. Some energy is absorbed by the most superficial tissues of the body such as skin.

Both machines have the capacity to create extremely detailed and revealing images. They generate outlines that reveal genitalia, buttocks, breasts, fat creases and all types of prostheses. The TSA has taken several steps to ensure the privacy of passengers—blurring the face, installing software to make the image less provocative, and ensuring that the operator never sees the passengers directly. Scans in airports cannot be saved or exported.

Another concern is the safety of the backscatter X-ray, which uses ionizing radiation. The potential for this to cause damage depends on dose. Low doses do cause biological damage, but the cells rapidly repair the damage. Moderate doses can change cells to become cancerous and can cause birth defects.

The dose of ionizing radiation emitted by the backscatter scan is extremely low—so low that it is really not known if there is a potential to cause harm. But even if the dose is low, the cancer risk merits consideration, given that there are 750 million enplanements in the US each year, and even a small risk per person could potentially translate into a significant number of cancers.

All of us are routinely exposed to ionizing radiation from many different sources—an average of 6 *milli*-sieverts (mSv) annually. The 2 most common sources are medical procedures

and ubiquitous background radiation (natural sources) from the sun and cosmic rays, and from the earth.. The backscatter X-ray scan exposes individuals to 0.03 to 0,10 *micro*-sieverts (uSv)—the equivalent of 3 to 9 minutes received from natural radiation in daily life.

One backscatter scan adds radiation equivalent to about 1 to 3 minutes of flight time.

A frequent flier would have to undergo 50 scans to equal the radiation from a dental X-ray; 1000 scans to equal that of one chest X-ray; 4000 to equal one mammogram; and 20 000 to equal a single abdominal-pelvic CT scan.

Extrapolating cancer risk from high levels of X-ray exposure to the small amounts of radiation from backscatter scan is questionable, and may be inappropriate. If one assumes a "linear-no-threshold" model (ie, there is no threshold) every exposure carries some risk.

The authors estimate that risk from a backscatter scan, given the limitations of cancer prediction, to be about 6 cancers over the lifetime of all US passengers. This contrasts with the hundreds of thousands of cancers that occur in the country every year.

Based on what is known about scans, passengers should not fear going through the scanners for health reasons, as the risks are truly trivial. However, continuing independent testing of the machines is necessary.

Conclusion: There is no significant threat of radiation from the scan.

I enjoyed this article, although it does not directly pertain to primary care medicine. Patients may ask about it.

It does contrast the concerns about very low doses of radiation from the scans with seeming unconcern about the relatively massive radiation doses from CT scans and mammograms.

As the authors mention, we can gauge the benefit / harm-cost ratio of backscatter scans. In my opinion, the benefit is great (peace of mind) and the harm nil. Costs may be significant, but when spread over millions of passengers, it becomes small.

ALCOHOL

2-2 ASSOCIATION OF ALCOHOL CONSUMPTION WITH SELECTED CARDIOVASCULAR DISEASE OUTCOMES

Possible cardioprotective effects of alcohol seen in observational studies continue to be debated. In the absence of clinical trials, clinicians must interpret observational data to answer

patients' questions about use of alcohol in relation to cardiovascular disease (**CVD**) and coronary heart disease (**CHD**).

This systemic review and meta-analysis analyzed 84 studies related to effects of alcohol on cardiovascular outcomes and death. All were prospective cohort studies. All subjects were age 18 or over, without preexisting CVD.

At baseline, compared active alcohol consumption with a reference group of non-drinkers.

Relative risks (**RR**) of events in alcohol drinkers vs non-drinkers:

	RR	
CVD mortality	0.75	In only one of 23 studies RR was over 1.00
Incident CHD	0.75	In only 2 of 32 studies RR was over 1.00
CHD mortality	0.71	
Incident stroke	0.98	
Stroke mortality	1.06	Null effect
Hemorrhagic stroke mortality	1.14	Possible harm
All-cause mortality	0.87	

Dose response (relative risks):

Alcohol dose grams per day vs no-alcohol

	CVD	CHD	
		Incident	Mortality
<2.5 g/d (< 1 drink)	0.71`	0.96	0.91
2.5 to 14.9 g/d (1 drink)	0.75	0.75	0.79
15 to 29.9 g/d (1-2.5)	0.75	0.66	0.79
30 to 60 g/d (2.5 to 5)	85	0.67	0.77
> 60 g/d (>5)	0.99	0.76	0.75
Sex			
Male	0.80	0.71	0.77
Female	0.69	0.71	0.78

Pooled estimates showed lower risk for drinkers vs non-drinkers (RR = 0.87). However the association was "J shaped". Those with the lowest consumption (< 1 drink daily) had a higher risk than those drinking 1 to 2 drinks daily. Risks then rose as quantity increased.

The protective association of alcohol has been consistently observed in diverse populations and
in both men and women.

The association is specific: moderate drinking (one drink daily for women and 2 drinks for men) is associated with lower risk of CVD, but is not uniformly protective for other conditions such as cancer.

The reduction in risk is notable, even when controlling for known confounders (smoking, diet,
and exercise). Any potential confounder would need to be very strong to explain away the apparently protective association.

Although there is great interest in differences between wine and spirits, alcohol drinking generally has similar effects on high density lipoprotein cholesterol. It is likely that any particular benefit of wine is confounded by diet and socio-economic status. This remains an important topic for further investigation.

Debate should center now on how to integrate this evidence into clinical practice.

Conclusion: Light to moderate alcohol consumption is associated with a reduction in multiple cardiovascular outcomes.

The consistency of the results is persuasive despite the risk of confounding.

Some authorities in the past have defined abstinence as a risk factor.

I believe this is the last work on this subject for a long time. A randomized controlled trial of alcohol ingestion would be impossible.

The studies must have average weekly consumption to calculate the daily consumption. I doubt all participants drank equal amounts every day. Consistently drinking small amounts of alcohol daily (a glass or 2 of wine with dinner) is the healthy way. Binge drinking (imbibing a week's ration of alcohol over the week-end) is related to increased risk of CHD.

***Increases High Density* Lipoprotein Cholesterol; Decreases Fibrinogen**

2-3 EFFECTS OF ALCOHOL CONSUMPTION ON BIOLOGICAL MARKERS ASSOCIATED WITH RISK OF CORONARY HEART DISEASE.

This systematic review concerned interventional (experimental) studies (1950-2009) of the effects of alcohol on 21 biological markers associated with risk of coronary heart disease (**CHD**).

The relevant biomarker:

A. Lipids (47 studies): triglycerides, total cholesterol, high density lipoprotein cholesterol (**HDL-c**), low density lipoprotein cholesterol (**LDL-c**) and apolipoprotein A1, Lp(a) lipoprotein

B. Inflammatory markers (13 studies): C-reactive protein, leukocytosis, interleukins, tumor necrosis factor.

C. Adipocyite hormones (8 studies): adiponectin, leptin.

D. Hemostatic factors (14 studies): Plasminogen activator, von Will brand factor, tissue plasminogen activator, plasminogen, fibrinogen, thromboxane, e-secretin.

E. Endothelial factors (3 studies): intracellular adhesion molecule, vascular adhesion molecule.

All were experimental studies involving alcohol interventions vs no-alcohol controls.

Alcohol consumption produced favorable changes in 4 biomarkers..

Pooled mean differences --alcohol vs no alcohol:

1) HDL-c	+ 0.09 mmol/L (+3.4 mg/dL*?
2) Apolipoprotein A1	+0.103 g/L
3) Fibrinogen	-0.20 g/l
4) Adiponectin	+O.56 g/L

(* My calculation ED)

There was s dose-response of HDL- to alcohol:

1-2 drinks daily	+0.072 mmol/L (2.3 mg/dL)
2-4	+ 1.03 (3.9 mg/dL)
> 4	+0.140 (5.3 mg/dl)

Alcohol produced no significant effect on LDL-c, triglycerides, total cholesterol, C-reactive protein,

or other biomarkers.

. “This meta-analysis showed that moderate consumption of alcohol up to one drink (15 g)

alcohol per day for women, and up to 2 drinks (30 g) alcohol for men have beneficial effects on a variety of biomarkers linked to risk of coronary heart disease."

The study also determined effects of different types of alcohol (wine, spirits, beer). All had similar effects on the biomarkers. The preference for using wine, and in most cases red wine as the type of alcohol for intervention may be related to other clinical characteristics.

The significant changes in levels of HDL-c, fibrinogen, and .adiponectin are well within a pharmacologically relevant magnitude.

"Although we found that alcohol consumption has favorable effects on some of the biomarkers
associated with coronary heart disease, this remains indirect evidence for the mechanism by which alcohol may cause cardiac protection"

ANXIETY DISORDER

3-4 EFFICACY OF DRUG TREATMENT FOR GENERALIZED ANXIETY DISORDER: Systematic Review and Meta-analysis

Generalized anxiety disorder (**GAD**) is a chronic or relapsing condition characterized by persistent and pervasive worrying and tension, which causes substantial personal distress and imposes a considerable economic burden.

Anxiety disorders are among the most prevalent of mental disorders and GAD is the most common and most impairing anxiety disorder in primary care. The degree of disability attributed to GAD compares with that of major depression and is similar to that of chronic physical illnesses such as arthritis and diabetes.

This systematic review included only double blind, placebo- controlled randomized trials of any
duration; and published systematic reviews and meta-analyses of randomized-controlled trials in adults receiving any drug for treatment of GAD. (1980-2009)

Data consisted of treatments and dosage, methods for diagnosis of GADS, duration, and relevant outcomes (anxiety scores at baseline and end of study, and proportion of responders and remitters).

The extracted data were combined in a series of mixed treatment meta-analyses, which incorporated evidence from trials, indirectly comparing drugs with a common comparator (such as placebo) as well as evidence from head-to-head trials. Application of this approach within a Bayesian framework enables treatments to be ranked in terms of the probability of each treatment being the first or most effective for each outcome measure.

Primary outcome measures:

1) Response: The proportion of patients who experienced at least a 50% reduction from the

baseline score on the Hamilton anxiety scale. *(Available on Google Ed.)*

2) Remission: The proportion of patients with a final score 7 or less. (Of 56)

3) Tolerability: Withdrawals because of adverse events.

Data from the 27 publications allowed analyses to be performed for 9 treatments: duloxetine, escitalopram, fluoxetine, lorazepam, paroxetine, pregabalin, sertraline, tiagabine, and venlafaxine. **1**

Probabilistic analysis of drugs by outcome measures.

(Figures in parentheses indicate percentage chance of being ranked first)

Rank	Response	Remission	Tolerability
1	Fluoxetine (63)	Fluoxetine (61)	Sertraline (49%)
2	Lorazepam (17)	Escitalopram (26)	Pregabalin (7%)*
3	Duloxetine (3)	Vnlafaxine (4)	Fluoxetine (38%)

4 - 9 All other drugs had a percentage probability of being first of 7% or less.

(*I do not understand this rating)

Fluoxetine was rated first in terms of response and remission. Sertraline was first for tolerability. (Ie, had lowest probability of withdrawals.)

All active treatments were favored over placebo. Placebo was favored over all treatments in terms of withdrawal.

Conclusion: In this study, fluoxetine was most effective in terms of response and remission, and sertraline was first in terms of tolerability.

1 Escitalopram [*Lexapro*]; fluoxetine [*Prozac*]; paroxetine [*Paxil*]; sertraline [*Zoloft*]; and venlafaxine [*Effexor*] are selective serotonin reuptake inhibitors. (SSRI) Duloxetine [*Cympalta*]is a serotonin,

norepinephrine reuptake inhibitor. Pregabalin [*Lyrica*] and tiagabine [*Gabitrile*] are antoconvulsants. Lorazepam [*Ativan*] is a benzodiazepine.

This is certainly not a definitive study. Placing fluoxetine [Prozac] and sertraline [Zoloft] first is tentative. Duration of the trial was short. This leaves the primary care clinician room to choose. I would choose the drug with which I was most familiar. If there were no choice, I would begin with Prozac at low dosage, then, if necessary, proceed with higher doses or switch to another drug. Fluoxetine has the advantage of being available at some pharmacies for $4.00 for a month's supply.

Drug therapy is not alone in treating GAD. A patient ear of the primary care clinician may help.

*The Hamilton Anxiety Rating Scale contains 14 questions related to anxiety, each having 0 to 4 responses, depending on severity of the symptom. (Total number of responses = 70, including zeros indicating the symptom is not present, to 4 indicating "*very severe".) *One questions asks specifically about depressed mood. Seven questions relate to somatic symptoms. I believe they may indicate some depression as well as anxiety.*

I abstracted the article in detail because it is the first example of mixed treatment meta-analysis I have encountered. I still do not fully understand it, but with time, I believe I will. I expect to see similar studies in the future.

ASPIRIN

1-5 WILL AN ASPIRIN A DAY KEEP CANCER AWAY?

Observational studies and randomized trials indicate that long-term aspirin use reduces incidence and mortality from colon cancer. Evidence of benefit from randomized trials for other cancers is limited.

A study in this issue of Lancet[1] provides important new evidence that long-term daily aspirin lowers mortality from several cancers other than colorectal cancer, and could have a meaningful effect on overall cancer mortality.

In eight randomized trials lasting up to 9 years, cancer mortality was 21% lower in the aspirin group than in the control group due mainly to a 34% reduction in colon cancer mortality.

In a longer -term analysis of 3 of the 8 trials, including 20 years of follow-up from the intervention and post-intervention periods, cancer mortality was 22% lower in those randomized to receive aspirin for 5 to 9 years than in controls.

The analysis of dose and duration of aspirin found that 75 to 100 mg daily seemed to be as effective as larger doses. However, even the lower doses of aspirin cause substantial risk of gi bleeding, possibly as much as 300 to 325 mg. No reduction in cancer mortality was noted in the first 5 years of aspirin use. Daily use for at least 5 years will probably be needed to reduce cancer mortality.

This contrasts with the results of the Woman's Health Study (2005), a large 10-year randomized trial of 100 mg aspirin taken every other day, which reported no benefit in overall cancer mortality. This might be explained by differences in the study population, by chance, or by the need to use aspirin daily to produce benefit.

What fatal cancers in addition to colon cancer might aspirin help to prevent? Benefits on esophageal, stomach, and lung cancer mortality seem likely. The reduction in esophageal cancer has been supported by observational studies. Reports of benefit on lung cancer have varied. Benefit was reported also in the Women's Health Study. Results for prostate and pancreatic cancers are suggestive, but should be interpreted with caution. Effects on prostate cancer mortality were not statistically significant. Pancreatic cancer mortality was significantly lower, but observational studies have not supported any effect.

Can we assume that, after 5 years of daily aspirin, an individual will experience a 34% reduction in the risk of fatal cancer as suggested by the intervention period analysis?

Assumptions about the exact magnitude of effects on cancer mortality should be made with caution. Confidence intervals indicate that the reduction in risk could plausibly be as low as 13%, and results for overall cancer mortality might not be completely generalisable to populations.

Clinical guidelines for aspirin use from the US Preventive Services Task Force recommend *not* using aspirin specifically for colorectal cancer prevention, and do not consider cancer when balancing the risk of serious gastrointestinal bleeding against the benefit from prevention of cardiovascular disease.

Lancet January 1, 2011, 377; 3 - 4 Comment by Eric J Jacobs American Cancer Society, Atlanta GA

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1 Lancet January2, 20111; 377: 31-41 "Effect Of Daily Aspirin On Long-Term Risk Of Death Due To Cancer" Original investigation, first author Peter M Rothwell, University of Oxford, UK

These investigators are justifiably enthusiastic about their work.

Investigators and journal editors persist in reporting benefits in terms of relative risk or hazard ratios. This can be very misleading. Patients maybe very impressed when told interventions X will reduce their chance of death by 33%. But less impressed when told they have less that one chance in 100 of benefiting.

However, they barely mentioned adverse effects of aspirin, although the trials were initially designed to prevent cardiovascular disease.

Primary prevention of CVD by aspirin has been discouraged because harm (mainly gi bleeding) outweighs benefits. Secondary prevention of CVD continues.

How should primary care clinicians respond to these findings?

At present, I believe harms will outweigh benefits. The NNT with long-term aspirin are very high, Indeed, much higher than most clinicians would judge to apply to practice. I expect bleeding would outweigh. benefit. Compliance with daily aspirin for years is problematic in primary care practice.

Perhaps some individuals who have a strong family history of gi cancer would be willing to risk possible harms of daily aspirin over 20 years.

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ATRIAL FIBRILLATION

5-5 MORTALITY RISK AMONG MIDDLE-AGED WOMEN WITH FIRST ATRIAL FIBRILLATION

An article in this issue of JAMA[1] provides evidence of increased mortality risk among middle-aged women with new-onset atrial fibrillation (**AF**).

During a median follow-up of 15 years, 1011 women developed AF. Sixty three deaths occurred.

In multivariable models, incident AF was associated with an increased adjusted risk of all-cause, cardiovascular, and non-cardiovascular mortality.

The Framingham Heart Study (**FHS**) demonstrated that the development of AF was associated with attenuation of the female survival advantage. The present study confirms that AF is associated

with premature death. Newly identified AF in seemingly healthy women should be taken seriously, and treated aggressively, recognizing that anticoagulation reduces stroke and mortality risk.

Compared with women who remained free of AF, those who developed AF had higher prevalence of hypertension, diabetes, hypercholesterolemia, smoking, and body mass index (BMI). This represents a high-risk group. While the cohort was event-free at baseline, whether these women could be considered "healthy" is questionable.

Why the increased risk of death with AF? It may be due to increased heart failure, stroke, and myocardial infarction.

Structural abnormalities are common in persons with AF: Dilated left atrium, left ventricular hypertrophy. In a study of lone AF, patients with normal-size atria had a long-time benign clinical course. Patients with increased atrial volume experienced adverse events. Left atrial enlargement is the common denominator for the pathological cascade leading to stroke, heart failure, and death. While it is important to link AF to death in middle-aged women initially free of cardiovascular events, it is equally important to recognize that almost half of the women in the WHS cohort who developed AF had an enlarged left atrium, and a third had left ventricular hypertrophy—a high prevalence of structural changes.

The prevalence of AF is often underestimated. Clinically, AF detection is far from straightforward. When AF is paroxysmal, it may not be discovered.

From a public health standpoint, clinicians should be aggressive in detection and treatment of AF. Anticoagulation and hypertension control in patients with newly identified AF was shown to reduce stroke incidence.

1 JAMA May25, 2011; 305: 2111-12 Editorial, first author Yoko Miyasaka, Kansai Medical University, Hirakata, Japan "RISK OF DEATH AND CARDIOVASCULAR EVENTS IN INITIALLY HEALTHY WOMEN WITH NEW ONSET ATRIAL FIBRILLATION"

The cohort consisted of 34 721 health care professionals in the Woman's Health Study (WHS) who agreed to prospective follow-up. They were age 49 to 59 (median 53) and free of AF and cardiovascular disease at baseline.

During a median follow-up of 15 years, 1011 (2.6%) women developed AF.

Incidence rate per 1000 person-years:

	AF	No AF

All-cause mortality	10.8	3.1
Cardiovascular mortality	4.3	0.57
Non-cardiovascular mortality	6.5	2.5

In the WHS cohort, at baseline, nearly half of the women who subsequently developed AF had hypertension, a third had hypercholesterolemia, and 9% were current smokers. (Were these women really "healthy" ?)

JAMA May 25, 2011; 305: 2080-87 Original investigation, first author David Conen, University Hospital, Basil, Switzerland

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AF is an important risk factor. Even if it is the sole risk factor (which it rarely is) it requires treatment. Combined structural heart changes and classical risk factors for CVD, increase risk.

5-6 NEW EUROPEAN GUIDELINES ON ATRIAL FIBRILLATION

The European Society of Cardiology has published new guidelines for managing atrial fibrillation (**AF**). Key changes include the identification of more people at risk of embolic stroke; wider use of oral anticoagulants; a more pragmatic approach to rate control; and a lower threshold for catheter ablation. (**CA**)[1] The priorities in management of AF are stroke prevention, rate control, and rhythm control.

Stroke prevention: To incorporate new evidence of the role of oral anticoagulants, the simple and easily remembered CHAD scoring system[2] has been modified.

Recommended anticoagulant strategy by CHA2DS2-VAS score:

0 No treatment (This is preferred to aspirin)

1 Oral anticoagulant preferred to aspirin; dabigatran 110 mg may be an alternative to warfarin.

2 and above: Oral anticoagulant. Dabigatran 150 mg may be an alternative to warfarin.

If aspirin is used for score of 0-1, a dose of 75 mg is reasonable because the risk of bleeding is dose dependent. But there is no evidence of an incremental reduction in stroke risk. Although aspirin is still considered a reasonable option in persons with a score 0-1, it is no longer the preferred option for most patients.

(Dabigatran, a direct thrombin inhibitor, has assumed a first place, replacing warfarin. The Europeans have had more experience with this drug than we have. Ed.)

Rate control vs. rhythm control: Rate control should be tried first, with rhythm control adopted for patients who remain symptomatic despite good rate control.

Rate control: The requirements for optimal rate control have been relaxed. One large trial compared lenient control aimed at a resting heart rate less than 110 vs. a resting rate of less than 80 with an increase of less than 110 with moderate exertion. New guidelines suggest lenient control initially and strict rate control in those who remain symptomatic. Beta-blockers remain the agent of choice for ventricular rate control. Non-dihydropyridine calcium blockers[3] are second choice, adding digoxin if needed.

Rhythm control: Paroxysmal AF can be eliminated by catheter ablation (**CA**) in 80-90% of patients, although up to 40% will require a repeat procedure. A 5% rate of complications compares favorably with long term antiarrhythmic drug therapy (eg, dronedarone; amiodarone, which have major adverse effects). The threshold for CA should be low. Guidelines therefore suggest it is a reasonable first-line treatment of rhythm control instead of drug therapy, especially in patients with NYHA grade III and IV heart failure..

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1 *Catheter ablation: A specially designed catheter is placed in a peripheral vein and directed to the right atrium. The atrial septum is pierced and the catheter enters the left atrium. The tip of the catheter is directed to the entries of the pulmonary veins into the left atrium. A heated end of the catheter destroys tissue around the entries, the source of the AF. (Obviously requires skill and experience.)*

2 *See the following full abstract for the updated Cha2DS2VAS. The score adds up to a maximum of 10 points. Very few patients with AF would have a score of 0. Almost all would receive anticoagulation.*

3 *There are about 20 dihydropyridine calcium blockers on the market. The suffix "dipine" denotes this class of drug (eg, amlodipine). Non-dihydropyridine calcium blockers are fewer in numbers (eg, varapamil; diltiazam). They produce a greater effect on the A-V node to slow ventricular rate in AF. Source: Wikpedia*
See the full abstract.

BREAST CANCER

At What Cost?

6-5 EXEMESTANE FOR BREAST CANCER PREVENTION IN PREMENOPAUSAL WOMEN

Estrogen contributes to normal breast development, and can also promote breast cancer (BC).

Aromatase inhibitors[1] (**AI**: eg, exemestane) profoundly suppress estrogen levels in postmenopausal women.

This international randomized, double-blind placebo-controlled trial (2004-2010) was designed to detect effects of exemestane in reducing risk of primary invasive BC.

All subjects (n = 4560) were postmenopausal (mean age 62). All were at increased risk of BC due to:

1) Age over 60
2) Gail risk score for BC greater than 1.66% chance (mean 2.3%) of invasive BC within 5 years (www.cncer.gov/bcrisktool)
3) Prior atypical ductal or lobular hyperplasia or lobular carcinoma in situ
4) Ductal carcinoma in situ treated with mastectomy

Randomized to:

1) Exemestane 25 mg/d +placebo
2) Placebo + placebo

Invasive BC at a median of 35 months number):

Exemestane 11

Placebo 32

The hazard ratio (treated vs placebo) = 0.35, a reduction in risk of 65%[2]

The number needed to treat (NNT) with exemestane for 3 years to prevent one BC = 94.

Exemestane reduced annual incidence of invasive BC from 0.55% to 0.19% and also reduced the incidence of known BC precursors (eg, ductal carcinoma in situ). This suggests possible further reductions in long-term incidence of BC.

Menopausal symptoms (hot flashes, sweating, insomnia) and arthritis were more common in the exemestane group.

Endometrial cancers and venous thromboembolism did not occur with exemestane.

Conclusion: Exemestane significantly[3] reduced invasive BC in postmenopausal women who were at moderate risk. During 3-years of therapy, there were no serious toxic effects and only minimal changes in health-related quality-of-life.

Clinicians should be aware of the cost component (to the patient and to society) of the benefit / harm-cost ratio of treatments they advise.

My pharmacist quotes a cost of $354.00 for 30 25 mg generic exemestane tablets.

= $11/80 per day per person

= $4,307.00 per year per person

= $12 921 for 3 years

= $29 521 485 to treat 2285 persons for 3 years

= $1 405 922 to prevent one BC over 3 years (21 of 2285 persons)

(This at a downside of frequent menopausal symptoms.)

1 *Some BCs require estrogen to grow.*

Aromatase is an enzyme that synthesizes estrogen.

The ovaries are the major source of estrogen in premenopausal women. In postmenopausal women, most estrogen is produced by conversion of androgen into estrogen by aromatase in percutaneous tissue (mainly adipose tissue) where it acts locally.

Circulating estrogen in postmenopausal women is the result of estrogen escaping local metabolism.

Exemestane (Aromatasin) is an aromatase inhibitor. It is used to treat postmenopausal BC. It is an oral steroid, which irreversibly binds to aromatase and inactivates it. The suppression rate is 85%for estradiol and 95% for estriol.

It is available as a generic. Source: Wikpedia

2 *Editors and authors persist in reporting risk reductions as percentages. This is clinically meaningless and misleading. The absolute risk reduction was about 1 per 100 treated for 3 years.*

3 *They also persist in mentioning "significance", meaning statistical significance, which can also be clinically meaningless and misleading.*

CAREGIVING

"Their Efforts And Their Well Being Are Too Often Ignored."

2-5 FULFILLING OUR OBLIGATION TO THE CAREGIVER

Family caregivers are relied upon by our health care system. They provide the bulk of care given to more than a million Americans with Alzheimer disease. At the same time, they are neglected.

They are expected to shoulder increasing amounts of complex care in the home, at minimal cost to the public, a task that would require entire health-care teams in the institutional setting.

In return, their efforts and their well being are too often ignored.

Family caregivers are often thrust into this position with no training and little support. This results in increased prevalence of adverse physical, social and psychological outcomes. Caregivers are at great risk for depression and anxiety. They are less likely to engage in preventive health measures. There is some evidence that they are subject to increased risk of mortality.

Caregiving for those with dementia requires considerable out-pf-pocket expenses. Many caregivers stop working in order to give care.

In the real world setting, little has been done to decrease caregivers' burdens.

What can be done to foster healthy caregiving?

Providing information about the skills and support systems needed to help caregivers for patients with dementia may be beneficial. Several different caregiver interventions have shown improvements in caregivers' well-being. They have been integrated with primary care.

Resources for Enhancing Alzheimer's Caregiver Health (REACH; a randomized trial) is an individualized multicomponent home- and telephone-based intervention designed to enhance caregivers' coping skills and management of dementia behaviors. The intervention improved caregivers' quality of life in terms of burden, depression, emotional well-being, self-care and healthy behaviors, social support, and management of problem behaviors. It also resulted in one hour less per day caregivers were required to provide care, giving them some respite.

Can these caregiver interventions be applied in the real world?

An article in this issue of Annals [*See abstract*]]describes application of an intervention similar to REACH. This program within the Veteran's Administration resulted in improved caregiver outcomes including reductions in caregiver frustration, burden, and depression.

Does the heath care system have a duty to provide caregiver support? The contractual obligation is to the patient. However, if the system will increasingly rely on family members to deliver complex care, then we have the obligation to aid the caregivers in their tasks and reduce their personal costs.

Interventions focused on caregivers are beneficial and can be practically implemented.

"It is time that we fulfill our obligations to caregivers."

Annals Internal Medicine February 28 2011; 171: 359-60 "Commentary", first author Eric Widera, University of California, San Francisco

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Caregivers do suffer; sometimes more than the care receiver. Their suffering is often inured.

I believe the first step primary care clinicians can take is to have a discussion with the caregiver, ask about and validate their degree of suffering. Ask them what they think can be done in their unique situation.

I doubt the public treasury will be able to support an expensive intervention described by REACH. Small Medical Homes probably could not afford the time and expense.

Perhaps other members of the family can help, if only allowing the principal caregiver to take a few hours off each day and have an occasional vacation. Perhaps Hospice can help.

Would employment of home health-care be possible?

C-REACTIVE PROTEIN

Benefits Of Statins Do Not Depend On CPR Levels

2-6 C-REACTIVE PROTEIN CONCENTRATION AND THE VASCULAR BENEFITS OF STATIN THERAPY The Health Protection Study [HPS]]

Inflammation is thought to contribute to the pathogenesis of coronary heart disease (**CHD**).

C-reactive protein (**CRP**) is an acute phase reactant synthesized by the liver. It is the most extensively studied marker of inflammation. A recent meta-analysis (2010) of 54 prospective observational trials reported that CRP concentrations were associated with risk of CHD. However, its associations with ischemic vascular disease were explained (confounded) largely by conventional risk factors. CRP is positively correlated with smoking, diabetes, BP, BMI, non-HDL cholesterol and triglycerides, and might not reflect causality.

The present randomized trial was undertaken in high risk patients in whom many vascular events took place during the study treatment period. This tested the hypothesis that the effect of statins differ according to the baseline concentrations of CRP and LDL-c.

Between 1994 and 1997, 20 536 persons age 40-80 (mean age 64) at high risk for vascular events
were recruited from 69 UK hospitals All had a previous diagnosis of CHD, occlusive disease of non-coronary vessels, diabetes, or hypertensive men over age 65. (A high-risk group.)

Randomized to: 1) 40 mg simvastatin daily, or 2) placebo. for 4 to 6 weeks.

The primary prespecified endpoint was major vascular events (coronary death, non-fatal myocardial infarction, fatal and non-fatal stroke, and coronary revascularization. (99% had complete follow-up for both mortality and morbidity.)

Duration of study = 5 years.

A total of 4518 (17%) major vascular events occurred over 5 years.

Overall, simvastatin resulted in a significant 22% reduction in the first major vascular events after randomization:

CRP level (mg/L)	Simvastatin (%)	Placebo (%)
<1.25	14.1	19.4
1.25-1.99	19.2	23.7
2.00-2.99	19.4	23.7
3.9904.99	23.0	29.5
5.00-7.99	25.6	30.6
>800	18.7	22.7
Total	19.8	25.2

There was no evidence that the proportional reduction in the endpoint or its components varied
with baseline CRP concentrations.

Even in participants with baseline CRP less than 1.25 mg/L, major vascular events were reduced
by 29%.

“In this study of more than 20 000 people at high risk of vascular events, 5 years of simvastatin

therapy reduced the risk of a major vascular event by a quarter, but there was no indication that the proportional risk reduction was larger in those with higher baseline CRP concentrations."

In participants with CRP concentrations less than 1.25 mg/L, or with low concentrations of both

LDL-c and CRP, there were significant reductions in the risks of major vascular events.

Hence, the present hypothesis-testing analysis, which is based on large numbers of major vascular events, does not lend support to the suggestion from hypothesis -generation studies, which included far fewer vascular events, that the beneficial effects of statin therapy are affected by baseline CRP concentrations.

The proportional reduction in the risk of major vascular events with statin therapy seem to be directly related to the absolute reduction in LDL-c that is achieved.

Conclusion: This large randomized trial does not lend support to the hypothesis that baseline CRP concentrations modify the vascular benefits of statin therapy materially.

I expect a rebuttal from CRP advocates.

No mention of adverse effects of simvastatin.

This study addressed secondary prevention. Results in primary prevention will vary.

As reported before, the benefits of statin drugs extend to additional lowering of initially low levels of LDL-c.

If this correction is sustained, it would be an excellent example of how misleading medical research can be, even though it is done in good faith and with care. Fortunately, in medicine, the truth will eventually out.

DABIGATRAN

5-4 ANTICOAGULANT OPTIONS—WHY THE FDA APPROVED A HIGHER BUT NOT A LOWER DOSE OF DABIGATRAN

In October 2010, the FDA approved dabigatran for the reduction of stroke and systemic emboli in patients with non-vascular artial fibrillation (**AF**). Approval was based on the RE-LY[1] study, which randomized patients to dabigatran 150 mg twice daily; dabigatran 110 mg twice daily; and warfarin titrated to an international normalized ratio (**INR**) of 2.0 to 3.0. Primary endpoint was stroke or systemic embolism

Both doses were non-inferior to warfarin in prevention of stroke and in risk of bleeding.

The 150 mg dose was significantly superior to warfarin in preventing stroke. Risk of bleeding was slightly less.

The 110 dose was associated with less bleeding than the other 2 drugs. Risk of stroke was slightly higher than the 150 dose.

Both doses would have been considered safe and effective if each of the doses were used alone in comparison to warfarin. In the end, the FDA approved only the 150 mg dose as showing clear superiority.

Patients and physicians value choice that allows treatment to be individualized. In patients for whom there is reason for heightened concern about bleeding, the low dose might have seemed desirable, even at the cost of higher risk of stroke.

Patients with impaired renal function (especially the elderly in whom AF is more common) have higher dabigatran blood levels and may be predisposed to bleeding. The low dose might offer advantages in these patients. Most people would agree that the irreversible effect of stroke has a greater clinical significance than nonfatal bleeding.

Warfarin is widely underused in patients with AF for a number of reasons including difficulty maintaining an INR within therapeutic range. Some may be willing to use dabigatran.

Efficacy and major safety outcomes in RE-LY

	110 mg	150 mg	Warfarin
% per year	(n = 601)	(n = 607)	(n = 602)
Stroke or systemic embnoli	1.5	1.1	1.7
Stroke Ischemic	1.3	0.9	1.1
Hemorrhagic	0.1	0.1	0.4
Systemic emboli	0.1	0.1	0.2
Major bleeding	2.9	3.3	3.6
Life threatening bleeding	1.2	1.5	1.9
Hazard ratio for stroke vs warfarin	0.74	0.52	

Hazard ratio for stroke 150 vs 110 = 0.72

Practical Pointers has abstracted several articles concerning the new anticoagulants (Factor Xa inhibitors as well as thrombin inhibitors). It may take a while to compare the benefit / harm-cost ratio of the various drugs.

Should primary care clinicians now begin to use these drugs? I believe prudence is needed. We need more time to determine safety, dosage, adverse events, and drug interactions. They certainly look promising.

Pradaxa is available at local pharmacies at the 150 mg dose. Cost is $278 for 60 tablets (one month's supply) —over $3000 per year. It can be obtained at a dose of 75 mg on special order.

1 RE-LY: Randomized Evaluation of Long-term Anticoagulation Therapy

"Dabigatran vs warfarin in patients with atrial fibrillation" NELM 2010; 361: 1139-51

Dabigatran (*Pradaxa*; Boehringer Ingelheim) is a direct thrombin inhibitor. It is given by mouth. It has an advantage over warfarin in that it requires no monitoring, and is less affected by dietary factors,

Absorption may be delayed by proton pump inhibitor and when ingested with fatty foods.

Some drugs will raise the blood levels.

It has been studied in prevention of thumbo-embolic complications of orthopedic and other surgeries.

It performed as well as the low-molecular weight heparin, enoxaparin.

Source: Wikpedia

DECISION MAKING

"Nothing About Me Without Me".

4-4 SUPPORTING PATIENTS TO MAKE THE BEST DECISIONS: Must be a Core Component of What it Means to be a Health Professional

"Imagine an intervention to improve patient care that systematic reviews have shown to be effective, does not seem to have any serious unwanted effectors, has been a central component of health policy for more than a decade, is popular with patients, and which in principle is embraced by most clinicians."

Such an intervention does exist.

It is shared decision making. This is a process in which patients are encouraged to participate in selecting appropriate treatment or management options on the basis of the best available evidence.

A defining mantra has become a central part of the current health reform: “Nothing about me without me”.

Patients involved in shared decision making are bettered informed than those who are not involved, and are less likely to be undecided about the best course of action. They are also more likely than the doctor to defer or decline surgical intervention, with no measurable adverse impact on health outcomes or satisfaction.

Clinicians are often poor at eliciting the patient’s agenda. One in three patients in primary care, and one in two patients in the hospital would have liked greater involvement in decisions about their care.

Shared decision making is a concrete manifestation of a more substantial social process, a re-conceptualization of the roles and responsibilities of patients and health professionals.

The interaction is increasingly being framed as a meeting between two experts. The clinician brings an understanding of the effectiveness, benefits, and harms of specific actions. The patient brings an understanding of preferences and attitudes to illness and risk.

Promoting shared decision making is increasingly seen as something that is needed to keep pace with changing social expectations.

The challenge for practitioners is to change attitudes and introduce new skills. Time and difficulty in access of high quality evidence are barriers.

Most fundamentally, the ability to share decisions must be seen as a core component of what it means to be a health professional.

Medicine’s most glaring failure has been our inability to convince the public to take better care of their health.

I was trained in the era of medical authoritarianism and paternalism. Often that was because patients and their physicians lacked choice of therapy. There was only one therapy or none. If no therapy was available, other choices had to be negotiated.

Now, the availability of choice and the ethical principle of autonomy have become the basis of the social change in medicine. There can be different approaches to a disease and its therapy, leading to the requirement of a choice based on shared decision making.

Shared decision is a process of negotiation. In primary care practice, negotiating a shared decision may at times be impossible. Not all patients are capable of understanding. Some are illiterate. Many may not realize they have a choice. There may be ethnic differences and language difficulties. Some are old, feeble and demented. They may not have a competent surrogate.

Not every consultation will involve shared decision making. The subject may not come up in many routine office visits in primary care, especially for short term care. The doctor's advice is often not controversial and is automatically accepted. The problem becomes more acute when decisions about end -of-life care, and cancer and other long term illnesses are debated. And when surrogates are responsible for decision making.

Physicians negotiate on the basis of probabilities and statistical reasoning, which the patient may not understand. Probabilities are based on randomized, controlled trials. Participants in RCTs often differ from the individual patient seen in consultation. Evidence may be conflicting. Pragmatic trials are rarely available The expertise required to apply the treatment suggested by RCTs may not be available locally. Drugs may be too expensive. Compliance may be too difficult for some. The probabilities cited by "the evidence" may not be applicable to the individual in his present situation.

Another side of the coin may present itself in primary care. Patients may forcefully present their autonomy. They may request (indeed insist upon) a new drug they saw advertised, ("Ask your doctor if X is right for you".) Here the doctor's autonomy comes forth. Doctors have autonomy too. If the drug is not appropriate, the primary care clinician should not prescribe it. Often, however, indication may be debatable, and the doctor may finally agree after informing the patient that adverse effects of new drugs may not be evident for years.

One negotiating point I have enjoyed is the "if" prescription-- for example, when a patient with a sore throat or bronchitis (which is most likely viral) insists on treatment with an antibiotic. The prescription is given with the restriction that it not be filled for a few days to give the illness time to settle. Many times the prescription will not be filled. It works.

How should the primary care clinician respond when the patient asks directly: What would you do? The question can be asked in two different ways.

1) What would you do if you had my illness?

2) What would you do if you were me?

It makes a difference.

See the following abstract—The Salzburg Statement

4-5 THE SALZBURG STATEMENT ON SHARED DECISION MAKING

In December 2010, 58 persons from 18 countries attended a Salzburg Global Seminar to discuss the role patients can and should play in healthcare decisions. They agreed on a statement that calls on patients and clinicians to work together to be co-producers of health.

We call on clinicians to:

- Recognize that they have an ethical imperative to share important decisions with patients.
- Stimulate the two way flow of information and encourage patients to ask questions, explain their circumstances, and express their personal preferences.
- Provide accurate information about options and the uncertainties, and benefits and harms of treatment.
- Tailor information for individual patient's needs and allow them sufficient time to consider their options.
- Acknowledge that most decisions do not have to be taken immediately, and give patients and their families the resources and help to reach decisions.

We call on clinicians, researchers, editors, journalists, and others to:

- Ensure that the information they provide is clear, evidence based and up to date and that conflicts of interest be declared.

We call on patients to:

- Speak up about their concerns, questions, and what's important to them.
- Recognize that they have a right to be equal participants in their care.
- Seek and use high quality health information.

We call upon policymakers to:

- Adopt policies that encourage shared decision making, including its measurement, as a stimulus for improvement.
- Amend informed consent laws to support the development of skills and tools for shared decision making.

Why?

- Much of the care patients receive is based on the ability and readiness of individual clinicians to provide it, rather than on widely agreed standards of best practice or patient's preferences for treatment.
- Clinicians are often slow to recognize the extent to which patients wish to be involved in understanding their health problems, in knowing the options available to them, and in making decisions that take account of their personal preferences.
- Many patients and their families find it difficult to take an active part in health care decisions. Some lack the confidence to question health professionals. Many have only a limited understanding about health and its determinants and do not know where to find information that is clear, trustworthy, and easily understood.

BMJ April 8 2011; 342:794

This may be a way to encourage patients to better care for their own health

DIABETES

A 50 Year Old With Diabetes Is About 6 Years Younger At The Time Of Death Than A Counterpart Without Diabetes.

3-1 DIABETES MELLITUS, FASTING GLUCOSE, AND RISK OF CAUSE-SPECIFIC DISEASE

The presence of diabetes doubles risk of a wide range of cardiovascular diseases. Diabetes is also associated with non-vascular disease.

This study aimed to provide a reliable estimate of independent associations of baseline diabetes and fasting blood glucose (**FBG**) levels with risk of cause-specific death.

The Emergent Risk Factors Collaboration analyzed data from 820 900 individuals--a total of

over 2 million person-years. The analysis focused on individual participant data from 97 prospective studies with information about the diagnosis of diabetes, and with information about FBG levels at baseline.

All studies included records of cause-specific deaths in participants who had accrued more than one year of follow-up. No participant had known previous vascular disease at baseline.

Assessed whether diabetes status and baseline FBG levels related to death from any cause, and main components including death from cancers, vascular diseases, and non-vascular conditions.

Calculated hazard ratios (**HR**; diabetes vs no-diabetes), pooled across studies.

Estimated cumulative survival from age 35 and older in those with and those without diabetes
at baseline.

Among the 820 900 participants, the mean age was 55; 52% male; 40 116 (6%) had diabetes at baseline. During 12.3 million person-years of follow-up, the median time to death was 13.6 years.

Hazard ratios for death after adjustment: [b]

	Diabetes vs no diabetes
All deaths	1.8
Cancer	1.25
Vascular	2.3
Non-vascular-	
Non-cancer [c]	1.83

(b. Adjustment at baseline for age, sex, smoking and BMI)

(c Deaths from renal disease, liver disease, pneumonia, other infectious diseases, mental disease, non-hepatic digestive diseases, external causes, intentional self-harm, nervous system disease, and COPD)

Fasting blood glucose and mortality: Levels exceeding 100 mg/dL, but not levels of 70-100 were associated with excess risk of death. As levels rose above 100, HRs for every 18 mg/dL rise, deaths increased by 1.05 for deaths from cancer, 1.13 for vascular, 1.10 for non-vascular, and 1.10 for any cause.

HRs for various FBG after excluding those with known history of diabetes (ie, self-reported) at baseline. As compared with FBG 70 to 100,

FBG 126 or more [d]	HR for death diabetes vs no diabetes
Cancer deaths	1.39
Vascular	1.89
Non-vascular; non-cancer	1.54

(d There was no formal (self-reported) diagnosis of diabetes, perhaps because the standards were not established at the time of the studies, or because the diagnosis was not made. Ed.)

FBG 100 to 125	HR for death
Cancer deaths	1.13
Vascular deaths	1.17
Non- cancer; non-vascular	1.17
Diabetes at baseline	
FBG less than 126	1.50
FBG 126 or more	2.16

In addition to the excess risk of vascular disease, diabetes is associated with substantial premature mortality from several cancers, infectious disease, external causes, intentional self-harm, and degenerative diseases, independent of several major risk factors.

On average, a 50 year old with diabetes, but with no history of vascular disease, is about 6 years younger at the time of death than a counterpart without diabetes.

The study did not observe appreciable alteration in the associations between diabetes and mortality after adjustment for several other risk factors (systolic BP, adiposity, inflammation biomarker, insulin, or renal function).

Conclusion: In addition to vascular disease, diabetes is associated with substantial premature death from several cancers, infectious disease, external causes, increased self-harm and degenerative disorders, independent of several major risk factors.

This massive and important study received input from experts in England, Scotland, USA, Sweden, Norway, and Iceland. It is all the more important for primary care because diabetes is largely a preventable disease.

Few patients' with diabetes realize the dangers of their disease. The authors state that death rates from diabetes are about equal to those of smoking.

I was not aware of the adverse effect of increased FBG, even at relatively low levels.

3-5 GLUCAGON-LIKE PEPTIDE-1 ANALOGUES FOR TYPE 2 DIABETES: A Review Article

Glucagon-like peptide-1 (**GLP-1**) is a naturally occurring peptide hormone released from the gut after eating.

GLP-1 has several important functions: 1) stimulates insulin secretion; 2) suppresses glucagon release (thereby reducing hepatic gluconeogenesis); 3) delays gastric emptying and promotes satiety.

It has a short half life (minutes) as a result of rapid breakdown by endopeptideases.

Two GLP-1 analogues (also known as incretin mimetics) are available for treatment of type-2 diabetes (**DM-2**) : exenatide and liraglutide. These are modified GLP-1 peptides which resist downgrading by endopeptideases. Their half-life is extended.

They are indicated as adjuncts to other treatments for DM-2.

The abstract discusses in more detail:

- Properties of
  - Exenatide (*Byetta*)
  - Liraglutide (*Victoza*)
- Safety issues
- Precautions
- Drug administration
- The future
- Costs

Practical Pointers has discussed GLP-1 analogues several times. They are an entirely new approach to treatment. Advantages include weight loss and low risk of hypoglycemia. If the costs come down and as long-acting preparations become more available, I believe they show great promise in treatment of DM-2.

Please read the full abstract for details. It condenses clinical information into a few pages.

The Goal Focuses On Quality Of Life And Symptom Management.

4-6 GLYCEMIC CONTROL IN FRAIL OLDER PATIENTS WITH DIABETES

More than 40% of adults with diabetes are older than 65. Many are frail with functional disabilities that limit their ability to live independently. Many live in nursing homes. Many are community-dwellers depending on others for care.

Large randomized trials examining the effects of glycemic control exclude elders. This has led to uncertainty regarding their appropriate level of glycemic control. Different guidelines recommend different targets. Guidelines generally agree on a target HbA1c of less than 7% for most adults. For frail older patients (**FOP**), The American Geriatric Society recommends a target less than 8%; the V.A. recommends 8% to 9%; the ADA recommends "less stringent glycemic control", not specifying the goals.

Most frail patients over age 65 with diabetes have competing risks for mortality that limit life expectancy and make vascular outcomes less important.

In FOPs, tight control often leads to substantial burdens (dietary restrictions, insulin injections, finger sticks, polypharmacy, and hypoglycemia).

The goal of care for FOPs focuses on quality of life and symptom management. Many of the interventions required for tight control are not consistent with these goals. Tight glycemic control imposes immediate substantial burdens with little chance of benefit.

The most appropriate glycemic target for FOPs depends on 2 factors: the degree of frailty and the outcomes that are most important for the patient.

By considering an individual older patient's frailty, life expectancy, and the special outcomes most important to the individual, clinicians can provide patient-centered care that appropriately balances the burdens and benefits of glycemic control.

This is an example of use of good clinical judgment.

I remember, way back when we knew little about diabetes (although insulin was available), one of my professors advocated treatment limited to relief to the classical symptoms of diabetes. (Thirst, hunger, weight loss, polyuria, glycosuria). This might now be a reasonable goal for FOPs.

DYING

Facilitating A Good Death Is A Core Clinical Role For Doctors

5-7 LET'S TALK ABOUT DYING

Imagine a situation where most persons with a common condition do not have it diagnosed. Where opportunities are repeatedly missed to identify the problem and offer structured evidence-based care. Where people are too often denied a chance to influence their care in a planned proactive way.

What is the condition?

Dying.

Despite huge advances and successes in end-of-life care, we have not yet managed to transform care of dying. Many of us are afraid to discuss dying, leaving patients unprepared and unable to plan. We must do more talking about it if we are to give patients the best chance of a good death.

People with advanced progressive illness who are admitted to the hospital are often not identified for end-of-life care. Many who could benefit from palliative care never have that opportunity. Too many people still die in distress with uncontrolled symptoms, are inappropriately resuscitated, and have futile interventions. Changes are needed to ensure that those at the end of life do not continue to be admitted to hospitals.

Often, despite multiple conditions, repeated admissions, and poor prognosis, patients are never formally identified for end-of-life care. One family member said " I wish the doctors had told me that my mother was dying".

Most people do not discuss their preferences for end-of-life care with their families. This hampers planning of care. Few British people have discussed with their family the type of funeral they want, whether they have a will, where they would like to die, or the type of care and support they would want at the end of life. Importantly though, people do want to talk to health professionals about dying. More than three quarters of people think that it is part of health professional's job to talk to them about where they would like to be cared for when dying, and where they would like to die.

This is crucial because, although most would like to die at home, most die in the hospital. A staggering 20% of hospital beds are occupied by end-of-life care patients who do not need or want to be there.

Facilitating a good death is a core clinical role for doctors. They should try to decrease patient's fear of dying, and increase awareness about palliative care.

BMJ May 2, 2011; 342: 1153 Commentary by Mayur Lakhani, general practitioner and chairman of Dying Matters Coalition and the UK National Council for Palliative Care

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This is the British experience. I believe the US experience is similar.

When and how to open the subject of dying may be difficult for many physicians. One suggestion I have read is simply ask "Are you at peace"? And go on from there.

Be mindful of ethnic differences. Some patients and families may be offended by the inference that death is near.

EFFICACY AND EFFECTIVENESS

One Of The Most Important Sources Of Clinical Uncertainty.

5-1 FROM EFFICACY TO EFFECTIVENESS IN THE FACE OF UNCERTAINTY

Clinical research is typically performed to address questions of:

1 Efficacy: Can it work in ideal settings?

2. Effectiveness: Does it work when generalized to the real-world and applied to individual patients?

3. Cost effectiveness: Is it worth it, and should it be paid for?

To date, research has been dominated by efficacy. It is not possible to provide reliable empirical evidence of effectiveness and cost-effectiveness on every question to guide decision-making. Instead, practitioners will continue to rely on inductive reasoning to apply the results of a study ("group averages" from efficacy trials) to individual patients who often differ in important ways from patients entered into efficacy trials. (Eg, patients may be older, have comorbid conditions, and using multiple medications.)

An insolvable problem then arises because there is no guarantee that the treatment effect observed in one group of patients can be repeated with certainty in a future patient. Decades of clinical experience have demonstrated that application of group trial data to individual patients is permissible by using efficacy as effectiveness data—provided there is a rationale for exchangeability of the past (the trial subjects) and future (your patient) events and the characteristics and circumstances of the subjects and the patient are sufficiently similar.

But, there is no precise resolution of what constitutes "sufficiently similar". Determination of similarity is often based on PICO: Whether characteristics between subjects in a trial and your patient

are similar enough to allow application of the trial results to individual patients in real world settings. This is a matter of judgment.

Patients (P)

Interventions (I)

Comparators (C)

Outcomes (O)

Relying on efficacy data to draw conclusions about effectiveness and the feasibility of application of trial data to an individual patient remains one of the most important sources of clinical uncertainty.
Indication creep:

Uncertainty is a key driver of the well-documented variations in the practice of medicine. Such variations commonly occur via so-called indication creep—the practice of promoting the use of an intervention for off-label indication. It is pervasive. When regulatory agencies approve a new drug, physicians are at liberty to administer the drug outside the approved indication provided they believe that doing so will benefit the patient.

Many off –label uses have been shown to have little or no scientific support. Indication creep is also inextricably linked to promotion of drugs by profit-driven industries.

Various mechanisms can lead to indication creep: Reducing the threshold for diagnosis, relying on surrogate endpoints, exaggerating efficacy and safety claims, and disease mongering. At its core, indication creep represents a shift from efficacy to effectiveness in an attempt to tailor research evidence to individual patients.

Prevention creep: The promotion of tests developed to detect symptomatic disease in asymptomatic patients.

For example:

When statins, which have proven highly beneficial in secondary prevention of heart disease, are extended for primary prevention in a population at low risk of heart disease.

When prostate specific antigen, which is important for detection of prostate cancer in symptomatic patients, is used for cancer screening.

When computed tomography, which is highly effective for cancer staging in patients with known disease, is promoted for detection of tumors in asymptomatic patients.

When chemotherapy, which is effective in management of advanced stages of cancer such as lymphoma or chronic lymphocytic leukemia, is increasingly used for treatment of minimal residual disease.

Uncertainty, Inescapable errors, Unavoidable Injustice

Judgments applied to extrapolation of evidence to individuals beyond the published limits of clinical trial data are inherently fraught with uncertainties. As a consequence, such extrapolation will not always be appropriate, resulting in inevitable error. Errors related to indication creep are typically:

1) False-positive error leading to *overuse* of health care interventions. (Inappropriate application of trial data to individual patients.)

2) False-negative error, resulting in *underuse* (failure to use an effective intervention).

Clinicians regret the consequences of unnecessary treatments (regret commission) less than the consequences of not administering treatments which would benefit (regret omission).

Overuse of health care interventions leads to squandering precious and finite resources. Because resources used for one group of patients cannot be used for another, indication creep inevitably leads to an increasing in health inequities and social injustice, and creates an acute ethical societal dilemma.

By decreasing false-positive error (*overuse*), social injustice can be minimized—distributing scarce health resources according to the principle of utilitarianism, emphasizing "the greatest food for the greatest number". However, this will lead to unavoidable individual injustice resulting from an increase in false-negative error (*underuse*) because those patients who might benefit from the appropriate use in off-label settings, or the administration of screening tests, will not receive them.

Indication Creep Belongs to the "No Technical Solution" Class of Problems

At present 30% of health care is inappropriate or wasteful. Given that 100% accurate decision-making is not possible, and that uncertainty, including error, must be considered facts of life, can the current situation be improved?

Curtailing commercial influence on prescribing and more comparative effectiveness research closely matched to PICO characteristics with individual-patient characteristics can help reduce indication creep. But physicians will never obtain empirical answers to all questions for caring for the patient. Physicians will always need to extrapolate beyond available evidence in their attempts to tailor treatments to individuals.

There is no technical solution to the ethical dilemma posed by indication creep. Any solution requires explicit consideration of the social values associated with the consequences of false-positive and false-negative errors. Any action may affect different individuals differently.

In the context of current indication creep, the public must understand that physicians are much more willing to tolerate false-positive errors (overuse) than false-negative error (underuse).

At present, squandering health resources appears to be more palatable than potential injustice to individuals by underuse.

JAMA May 18, 2911; 305: 2005-06 Commentary, first author Benjamin Djulbegovic, University of South Florida, ,Tampa

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This is a thoughtful and important article. It describes the present state of primary care. It discusses the "art " of medicine-- the application of medical science to individuals, all different.

We cannot predict effectiveness to individual patients. They will vary in some ways (perhaps in most ways) from subjects entered into trials.

Trials often report benefits as a percentage of the subjects entered. If only 10% of subjects benefited in a trial, how can we predict which individual patient will benefit?

Cost effectiveness is often neglected in individual patients. Does the prescriber know the cost of the drugs he prescribes? Can the patient afford it? The best application of evidence-based medicine and the best of drugs are meaningless if the patient cannot afford them.

Primary clinicians must know as much about the characteristics of individual patients as they know about their disease and the applicable trials.

Can this treatment help my patient?

What is the probability it will help?

What is the harm?

How much does it cost?

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HEMOGLOBIN A1c

MmolHbA1c/mol Hb A

5-3 HbA1c: AN OLD FRIEND IN NEW CLOTHES

The units of HbA1c have changed.

The way in which we use and interpret glycated hemoglobin A1 measurement is also changing. New guidances for the diagnosis of diabetes include HbA1c.

HbA1c was discovered in the 1960s through the electrophoresis of hemoglobin. Routine measurement was applied into clinical practice in the 1990s after the Diabetes Control and Complications Trial (**DCCT**).

The use of HbA1c in the diagnosis of diabetes is controversial, although a 2009 expert consensus strongly advocated measurement of it for this purpose.

The International Federation of Clinical Chemists (**IFCC**) has altered the units in which HbA1c is reported by replacing the traditional percentage units with standard mmolHbA1c/mol Hb A (mmol/mol) measurement. This may be confusing.

Why the change? Lack of agreement of HbA1c among laboratories has long been a concern. A reference method remained undefined. The IFCC has produced a purified preparation of HbA1c, which enabled development of a reference method.

The new preparation showed a 1.5% to 2% lower HbA1c level than the traditional HbA1c. This discrepancy may result in patients and clinicians mistakenly believing that glycemic has improved. To reduce confusion, the ISCC has changed its unit of measurement from percentage to mmol of HbA1c per mol of hemoglobin A (mmol/mol).

Clinicians should resist converting mmol/mol back to DCCT-aligned percentage units. This comparison should be used only to educate patients about the key target in the new units –less than 6.5% of HbA1c becomes less than 48 mmol/mol.

The DCCT-aligned results are now effectively meaningless.

In 2009, the American Diabetes Association and the WHO proposed HbA1c as a diagnostic criterion for diabetes, suggesting a cut-off greater than or equal to 48 mmol/mol as being diagnostic.

One untimed, non-fasting blood sample has clear advantages. HbA1c concentration varies less within the same individual than fasting glucose or the glucose tolerance test.

However, HbA1c is affected by red-cell turnover (anemia), age, ethnicity, and genetic polymorphisms. The assay is also subject to interference from hemoglobin variants (sickle cell) and derivatives resulting from renal failure and drugs.

Can HbA1c concentrations below a given threshold exclude diabetes on the basis of one sample in an individual with unknown hemoglobin phenotype and unknown renal or iron status? Potential interference needs to be identified. The trend in HbA1c, rather than the absolute value, is of primary interest when HbA1c is used for glycemic monitoring. It is crucial to identify these interferences when a single HbA1c is used for diagnosis.

In June 2011, the DCCT units will cease to be co-reported.

It is time to reset our minds.

Lancet April 30, 2011; 377: 1476-77 First author Shivoni Misro, Imperial Health NHS Trust, London, UK

Equivalent DCCT-aligned and IFCC-standardized values:

DCCT (%)	IFCC (mmol/mol)
5	31

6	42
7	53
8	64
9	86
10	108

I have yet to see any mention of the new standards in the articles about diabetes I abstract. What now is the place of fasting blood glucose? Is the glucose tolerance test obsolete?
What about home glucose monitoring?

HERPES ZOSTER

Confirming the Effectiveness of the Vaccine

1-6 HERPES ZOSTER VACCINE IN OLDER ADULTS AND THE RISK OF SUBSEQUENT HERPES ZOSTER DISEASE

The pain of HZ is often disabling and can last for months or even years. Approximately 1 million episodes of HZ occur in the US annually.

This randomized cohort study (2007-2009) compared 75 781 persons who were given HZ vaccine
with 227 283 matched controls. All who received the vaccine were community dwelling and immunocompetent and age 60 and over.

This study evaluated the effectiveness of the vaccine under field conditions. (Ie, the effect when the vaccine is applied by primary care clinicians to the general population.).

	Vaccinated	Not vaccinated
Follow-up (mean-years)	1.72 y	1.56 y
Overall incidence of HZ	828 of 75 781	4606 of 227 283
%	1.09	2.03
Absolute difference	0.94%	
Incidence per 1000 person-years	6.4 %	13.0%
NNT	106	
Hazard ratios		

HZ	0.45	1.00
Ophthalmic HZ	0.37	1/00
Hospitalizations for HZ	0.24	1.00

Among unvaccinated persons incidence of HZ was more common in those over age 80, in women,
and whites.

Overall, herpes zoster vaccine was associated with a 55% reduction in incidence of herpes zoster, which is consistent with the 51% vaccine efficacy reported from the original vaccine study. (2005)

The vaccine has the potential to prevent tens of thousands of cases of HZ and postherpetic neuralgia.

The Advisory Committee for Immunizations Practices recommends it for all healthy individuals over age 59.

Conclusion: Among immunocompetent community dwelling adults age 60 and older, the vaccine was associated with lower incidence of HZ Risk was reduced among all ages, and among individuals with chronic diseases.

HZ is a disease of waning immunity. It is growing as the present old generation grows older. For following generations, which have the advantage of receiving chicken pox vaccine in childhood and never experienced the disease, incidence of HZ may decrease markedly.

The HZ vaccine is good, but not perfect. Uptake by the public has lagged. I believe medical profession has failed to stress its importance.

I had forgotten how the terms were coined:

Herpes: herpein Gr. to crawl; Zoster: Gr. Belt or girdle

Shingles: L.: cingulus belt

4-8 FDA EXPANDS AGE RANGE FOR SHINGLES VACCINE

Shingles vaccine (Zostavax: Merck; a live varicella-zoster vaccine) is now approved for persons age 50-59 as well as older persons. The FDA made this announcement in late March 2011.

The availability of the vaccine for younger persons provides an additional opportunity to prevent the disease.

The FDA based its decision on a multicenter randomized trial of about 22 000 patients age 50-59. Half received vaccine; half placebo. After a year, the vaccine reduced risk of shingles by about 70% compared with placebo.

In the USA, about 200 000 persons age 50-59 develop shingles each year.

Unfortunately, the vaccine can also trigger development of shingles. The cause is not known. The most common adverse effects are redness and pain at the subcutaneous injection site, and headache.

Patients who are immunocompromised should not receive the vaccine. This includes those with AIDs, lymphoma, cancer of the bone or blood, and those undergoing radiation therapy and those receiving corticosteroids.

JAMA April 20, 2011; 305: 1526 "Medical News and Perspective", comment by the JAMA staff.

Shingles provoked by the vaccine can be very severe and disabling. There is no way of predicting.

Children now receive chickenpox vaccine. They will never develop chickenpox, and will not harbor the virus. . Will shingles disappear? The vaccine virus is live.

HYPERTENSION

. ***"Important Implications For Diagnosis And Treatment Of Hypertension."***

2-1 CONVENTIONAL VERSUS AUTOMATED MEASUREMENT OF BLOOD PRESSURES IN PRIMARY CARE PATIENTS WITH SYSTOLIC HYPERTENSION

There is concern about the accuracy of the measurement of BP in "real life" clinical settings. Imprecise and inconsistent measurements are often reported**.** Proposals for improved assessment include greater reliance on home and 24-hour monitoring. Out-of-office determinations lower risk of a spurious higher than usual BP due to the "white coat" effect (**WC**).

Use of automated office sphygmomanometers provides a third option for accurate assessment of BP.

Measurement of BP with the patient sitting quietly alone eliminates patient-observer interactions such as conversation, an important cause of WC effect.

This trial was designed to evaluate the effect of automated office versus usual office BP on the management of hypertension (predominantly systolic) in routine practice.

Entered 555 primary care patients with systolic hypertension. All were over age 45. None had serious comorbidities None were using home BP measurements. All underwent ambulatory 24-hour BP measurement before randomization, with special attention to awake BP.

Randomized to: 1) Ongoing use of manual office BP measurement (controls) or 2) Automated office BP determination (interventions). Used an automated BP machine which determined 6 readings 2 minutes apart. The attendant left the room after the first reading, which was disregarded. The patient sat quietly alone while the 5 remaining readings were taken.

Main outcome = difference in systolic BP between groups.

Comparison of intervention group vs control group:

	Automatic office	Usual manual office
Last routine manual systolic	149.5	149.9
Office systolic after enrollment	135.6	141.4
Difference from last manual	-13.9	-8.5 (A 5.4 mm difference)

(Automated office readings resulted in about a 5 mmHg lower systolic compared with routine office measurement.)

Comparisons with pre-test 24-h ambulatory systolic (awake hours):

Post entry systolic	135.6	141.4
Pre-entry awake 24-h ambulatory	133.2	135.0
Difference between pre-entry 24-h awake systolic and test groups	2.4	6.54

(The office automated readings were closer to the ambulatory awake BP than the usual office readings.)

"This trial provides important and robust evidence supporting use of automated office BP

measurements in routine practice."

Replacement to manual office BP determinations with automated office determinations virtually eliminated the WC effect. Automated determinations also showed a stronger correlation with awake ambulatory BP than did manual readings.

The net reduction in BP attributed to the automated group can be calculated at -5.4 mmHg. This is of considerable clinical importance.

Recently the American Heart Association recommended use of home BP monitoring. "Every hypertensive patient should purchase a home BP recording device. "

"This study has important implications for diagnosis and treatment of hypertension."

Conclusion: In compliant otherwise healthy primary care patients with systolic hypertension, introduction of automated office BP measurement significantly reduced the white coat response compared with ongoing use of manual office BP measurement.

Improvement of BP determinations are bound to improve over time

I believe most patients could learn to relax while taking a series of home BP measurements. Patients will likely note that BP declines with repeated determinations.

It would be interesting to ask patients to take 6 readings a few minutes apart and discard the first. However, these investigators mentioned that simply pushing a button on a home BP machine will raise BP.

Only24-hourambulatory measurement will determine "masked hypertension" an opposite of WC in which ambulatory BP is higher than office BP.

"Significant Benefits from Antihypertensive Treatment"

3-2 ANTIHYPERTENSIVE TREATMENT AND SECONDARY PREVENTION OF CARDIOVASCULAR DISEASE EVENTS AMONG PERSONS WITHOUT HYPERTENSION: A Meta-analysis

Prospective studies have established a strong, graded, and independent positive association between BP levels and risk of CVD, stroke, and premature death. Increased risk of CVD begins at systolic as low as 115. Many strokes and CVD events occur in patients with systolic BP less than 140.

More than 30% of the general population has prehypertension. (BP 130-139/86-89)

In persons with prehypertension, about 90% have at least one risk factor for heart disease or stroke.

Clinical trials have documented that lowering BP reduces CVD mortality among patients with hypertension. Several randomized trials of lowering BP for prevention of CVD have demonstrated benefit among persons with prehypertension, and even in those with normal BP. Others have shown no benefit.

This meta-analysis evaluated the association between antihypertensive treatment and secondary prevention of CVD events and all-cause mortality among persons without clinically defined hypertension (lower than140/90).

Extensive search discovered 874 possibly relevant randomized-controlled trials. Of these, 25 were included in the meta-analysis. All were limited to individuals over age 19. Antihypertension treatment, entry criteria, and duration varied between trials. Mean age varied between 55 and 68; 75% were male.

All subjects had a history of CVD: clinical evidence of recent myocardial infarction (**MI**), congestive heart failure, coronary artery disease, stroke, or the CVD equivalent--type-2 diabetes. (To classify the study as secondary prevention.)

The 25 studies incorporated data from 64 162 participants, all had a baseline BP under 140/90.

Pooled overall relative risks (**RR**) and absolute risk reduction: (Treatment vs placebo)

	RR	Absolute risk reduction per 1000
Stroke	0.77	-7.2
MI (fatal and non-fatal)	0.80	-13.3
Congestive heart failure	0.71	-43.6
Composite CVD outcomes	0.85	-27.1
CVD mortality	0.83	-15.4
All-cause mortality	0.87	-13.7

The overall pooled results from antihypertensive treatment, compared with control, showed a significant reduction in risk for stroke, CHF events, CVD events, and all-cause mortality.

Conclusion: Prehypertension affects nearly 1/3 of the adult population, and carries an elevated risk for CVD incidence and mortality. Among patients with a clinical history of CVD,

but without hypertension, antihypertensive treatment was associated with decreased risk of stroke, CHF, CVD events, and all-cause mortality We do not know if benefits occur in patients without CVD.

So, what is "hypertension"?

What is prehypertension? [1]

What is normal? (Normal systolic then could be 115 to 129; or 115 to 119)

Do we really have good definitions? Presently they are defined by arbitrary cutpoints. If prehypertension is 120-130, and hypertension begins at 140, normal must be narrowly defined as 115-119.

I believe hypertension may be defined as the BP level, which in an individual causes organ damage, or is associated with increased risk of organ damage.

The likelihood of organ damage determines the benefit / harm-cost ratio of drug therapy. An assessment of the benefit / harm-cost ratio is essential for every patient.

When systolic is below 140, I doubt BP is the predominant risk factor.

All risk factors must be treated. Lifestyle intervention is the predominate therapy, especially in younger patients. Prescribing drugs to younger patients would expose them to adverse effects and costs of drugs over a longer time. Older patients are more at risk for CVD events. For them, drug therapy would be more beneficial, and would be taken for a shorter time.

This study assessed treatment of prehypertension in patients who had established CVD. What about patients who have a long list of risk factors and have no history of CVD events? Certainly, they are at increased risk compared with those who have few risk factors. Would preventive measures be termed primary prevention or secondary prevention ? How about tertiary prevention?

Prehypertension and hypertension (plus other risk factors) in our population are so common as to be almost universal. This raises the issue of universal treatment with a "polypill".

1 *The article defines systolic for prehypertension as 130-139; the editorial as 120-139 JNC VI defined prehypertension systolic as 130-139. JNC VII as 120-139. (Personal communication with Lydia A L Bazzano, MD, PHD, Tulane University)*

The A,B,C,Ds Of Drug Treatment For Hypertension

4-3 ANGIOTENSIN CONVERTING ENZYME INHIBITORS AND ANGIOTENSIN RECEPTOR BLOCKERS IN HYPERTENSION

First-line antihypertension drugs are classified as A,B,C,D. Drugs classified as A include angiotensin converting enzyme inhibitors (**ACE**) and angiotensin II receptor blockers (**ARB**). B drugs are beta-blockers (**BB**); C are calcium antagonists; D are diuretics. A,B,C,D is a helpful mnemonic to use in initial treatment as well as adding a second drug when needed. It is used in UK guidelines to manage hypertension in primary care.

Beta blockers have fallen out of favor as single agents for treatment of hypertension when the BP is the only problem. This leaves A, C, and D as the main drugs to start treatment.

Patients with normal or raised plasma renin levels (eg, many young adults with essential hypertension) do better with A and B drugs. Those with low renin levels (patients of African descent and older patients) respond well to C and D.

This article focused on use of ACE or ARB when starting treatment.

ACE and ARB relax blood vessels and promote excretion of sodium, reduce cardiac preload and afterload, and lower BP especially in patients in whom the renin-angiotensin-aldosterone system is activated.

The article discusses:

How do ACE and ARB compare with other antihypertensive drugs?

How well do ACE and ARB work?

Combination treatment with ACE and ARB

How safe are A drugs? (Adverse effects)

What are the precautions when starting ACE or ARB?

How cost-effective are ACE and ARB?

How are ACE and ARB taken and monitored?

This is an excellent review and reference article for primary care. Please read the full abstract. It presents general comments about treatment of hypertension, as well as detailed information about ACE and ARB

Since most hypertensive patients in primary care are over age 55, C and D drugs are the preferred drugs.

6-1 NEW GUIDELINE COVERS WAYS TO PREVENT AND TREAT HYPERTENSION IN ELDERLY PEOPLE

For the first time, clinicians have a guideline on the prevention and treatment of hypertension specifically in individuals older than 65. This came in April 2011 from the American College of Cardiology and the American Heart Association.

Although hypertension is prevalent in this older population (64% of men and 78% of women) control is less common. Many clinicians are reluctant to treat these patients because they believe it will increase mortality. Moreover, rigorous study of hypertension in those over 80 has been nonexistent.

A study in 2008 (Hypertension in the Very Elderly Trial [HYVE][1] changed the landscape. It looked at 3845 patients, age 80 and over, randomized to antihypertensive therapy with a diuretic and, if necessary to reach target, an added angiotensin converting enzyme (ACE) inhibitor.

Compared with the placebo, the active treatment reduced systolic BP by 15 mmHg with a reduction in the rate of death from cardiovascular causes of 23% and a 21 % reduction in death from any cause.

The trial was stopped for ethical reasons at the end of 2 years. The findings were compelling enough to warrant new guidelines. However, the lack of rigorous research on prevention and management of individuals age 65 and older with hypertension resulted in the panel's statement that the recommendations were based largely on expert opinion.

(Go to the full abstract to access the guideline Ed.)

JAMA June 15, 2011; 305: 2394 "Medical News and Perspective" by Mike Mitka, JAMA staff

1 "Treatment of Hypertension Patients 80 Years of Age and Older" NEJM May 1. 2008; 358: 1887 First author Nigel S Beckett, Imperial College, London.

This international trial randomized 3848 patients age 80 and over who had a sustained systolic BP 160 and over to receive either a diuretic (indapamide) alone or with, if necessary, an added angiotensin converting enzyme (ACE) inhibitor (perindopril) vs placebo. Target was a systolic of 150.

At baseline, mean age was 83, mean systolic BP 173. At 2 years mean systolic was 15 mmHg lower in the active treatment group than in the placebo group.

In the intention-to-treat analysis, active treatment was associated with a 30% reduction in fatal or non-fatal stroke, 21% reduction in death from any cause, a 23% reduction in death from cardiovascular causes, and a 64% reduction in heart failure.

Few serious adverse effects were reported.

The investigators concluded that antihypertensive treatment in persons over age 80 is beneficial.

This is another example of investigators and editors reporting benefits in terms of percentage reduction in risk. This looks impressive but may have little clinical meaning.
To detect absolute risk reductions, readers must go to the data published in the article and calculate it themselves.

According to my calculations, for every 1000 persons treated for one year, 5 patients would avoid stroke, 5 would avoid death from any cause, 7 avoid any CVD event, and 10 avoid heart failure.

Considering the severity of these outcomes, I believe treatment is worthwhile.

Journals almost always cite BP as systolic / diastolic. And almost always the diastolic is irrelevant, especially for patients over age 50. Outcomes depend on systolic. Patients get confused when told their BP is X/Y. What is systolic? What is diastolic? They will understand more clearly and remember when told their BP is X.

What is "hypertension" ? At present, the best we can do is to define it as a number. Alternatively, hypertension could be defined as that BP, which in an individual will increase risk of organ damage, mortality, and morbidity.

Decision about whether, and how, to treat a given BP in an elderly person would then become a matter of clinical judgment instead of depending on numbers. Certainly, many persons over age 80 should not be treated.

The subjects in this trial were generally in good health for their age.

If the decision is made to treat, I believe home BP monitoring is essential to guide therapy.

"It's Time To Get Serious About BP Measurement"

6-2 IMPROVING THE MEASUREMENT OF BLOOD PRESSURE: Is it time for regulated standards?

Ideally, BP should be measured using an appropriately-sized cuff, with the patient resting for 5 minutes in a seated position, with the feet on the floor, with the back supported.

Deviations from this standard are common. In practice, BP measurements are remarkably casual. Cuffs are applied over clothing. BP is obtained without allowing the patient to rest. Measurements are taken while patients are sitting hunched over the examining table with their legs dangling. Training is minimal. Devices are not checked, and not recalibrated.

Even in research settings, the most experienced personnel can become sloppy, as manifested by digital preference—an unexpected high percentage of readings ending in "0".

Frequency of measurement also matters. Random measurement error and inherent biological fluctuations lead to within-patient variability of measurement. Assessment of BP requires several measurements over separate patient encounters. Averaging BP across several clinic visits enhances precision even more than several readings at a single visit.

The percentage of patients with controlled BP (< 140) may vary with the type of measurement. A study in this issue of *Annals*[1] reported 28% of patients were considered controlled by clinic measurements; 49% by home measurements; and 68% by research methods. Only 33% of patients were correctly classified as having BP that was in or out of control. A single measurement of 120 to 157 was not sufficiently precise to correctly classify a patient as having BP that was in control with 80% certainty.

Greater precision (lower within-patient variation) can be obtained with additional measurements. This benefit was present when the measurements were taken at up to 4 visits. There was little benefit in additional measurements. (Averaging BP across visits reduces within-patient variability.) However, the cost and patient-burden of several visits is of concern. Hence determination of BP at home will benefit by enabling repeated measurements. Reasons may be—elimination of the white coat effect, and clinic measurements that do not conform to recommended standards.

The implications of this discordance are substantial for both patients and clinicians. Spuriously high clinic readings could lead to inappropriate escalation of drug treatment and adverse effects.

The importance of accurate BP measurement has largely been neglected. High quality measurements should be averaged over several visits

"It is time to get serious about BP measurement."

Annals Internal Medicine June 21, 2011; 154: 838-39 Editorial, first author Laurence J Appel, Johns Hopkins University, Baltimore MD.

1. "Measuring Blood Pressure for Decision-making and Quality Reporting: When and How Many Measurements?" Original investigations, first author Benjamin J Powers, Durham Veterans Affairs Medical Center, Durham NC

This strengthens my belief that home BP measurement is necessary for good BP control. The usual busy primary care office may not take time to assess BP properly. Home measurement can be done with the patient relaxed and in the proper position. Multiple readings can easily be taken and averaged over time.

My experience with home BP—the third reading in a 10 minute series is often the lowest.

The article did not mention diastolic pressure. I believe only systolic is important in the vast majority of older patients seen in primary care. Focusing on systolic will save time and avoid patient-confusion.

IRRITABLE BOWEL SYNDROME

1-4 ANTIBIOTIC THERAPY FOR IRRITABLE BOWEL SYNDROME

The irritable bowel syndrome (**IBS)** is one of the most common conditions seen in primary care practice. Treatment is limited because of lack of understanding the pathophysiology of the syndrome, which is probably heterogeneous.

Alterations in the bacterial flora of the bowel are being considered a possible pathogenic factor.

Probiotics have been studied as treatment, but improvement is limited.

A study in this issue of NEJM[1] reports the results of 2 identically designed large double-blind placebo-controlled studies of rifaximin[2] in patients with IBS without constipation. Randomized over 1200 patients to 1) rifaximin three times daily. or 2) placebo for 2 weeks, followed by 10-week post-treatment observation.

The primary end-point was the proportion of patients who reported adequate relief of symptoms assessed by a questionnaire.

A key secondary end-point was adequate relief of bloating.

Rifaximin is a poorly absorbed broad spectrum antibiotic acting against gram positives and gram negatives, including *C difficile* and anaerobes It is extensively used for traveler's diarrhea. It has a favorable safety profile, low risk of side effects, and low risk of producing bacterial resistance.

In both studies, rifaximin vs placebo patients consistently met the criteria for relief of global IBS symptoms (41% vs 32% for placebo) and IBS-related bloating (40% vs 30%) for at least 2 of the first 4 weeks. Similar benefits were obtained for relief of IBS symptoms. during the 10-week post-treatment period, although benefits in both groups gradually decreased.

The advantages of the drug are the short treatment period, the sustained beneficial effects for 10 weeks, and the benefit on reducing bloating, which is one of the most challenging symptoms of IBS.

But the therapeutic gain of treatment in providing adequate relief ranged between 9% and 12 % compared with placebo. This is at the lower spectrum of what is considered clinically relevant. (NNT = 10)

IBS is a chronic disorder. Although benefit persisted after a 2-week treatment period, the response over time suggests some loss of efficacy toward the end of 10 weeks. It is not known if patients will benefit from a second course of therapy.

The mechanism of action is controversial. Initial studies of absorbed antibiotics were based on the hypothesis that these patients have small intestinal bacterial overgrowth. But later studies with jejunal aspiration and bacterial culturing did not support the theory. The most likely mode of action of rifaximin is a reduction in the overall bacterial load, especially in the large bowel. This may led to less bacterial fermentation and less bloating, possibly combined with decreased secretion of bacterial products that contribute to the generation of symptoms.

At present rifaximin is not approved for the treatment of IBS. FDA approval is pending.

The drug has the potential to provide a welcome addition to the limited number of drugs that are available to treat IBS. It has a favorable safety profile. No treatment -associated cases of C difficile colitis have been reported.

Presently, clinicians should proceed with caution in using this drug. IBS is a chronic condition. The efficacy of rifaximin used repeatedly or chronically for treatment of IBS is not known. The risk of bacterial resistance may be high.

It may be reasonable to try one course for treatment of IBS in patients without constipation who have failed other treatments.

NEJM January 6, 2011; 364: 81-82 Editorial by Jan Tack, University of Leuven, Belgium
1. "Rifaximin Therapy for Patients with Irritable Bowel Syndrome without Constipation" NEJM January 6, 2011; 364: 22-32 Original investigation, first author Mark Pimentil, Cedars-Siani Medical Center < Los Angeles.

At the end of the 2 weeks, active treatment provided benefit in 48% vs 41% in the placebo group. At the end of the trials (12 weeks) 34% vs 26%. [My assessment of figure 4 page 30]

The placebo response was high. Benefit of rifaximin remained higher than placebo over 12 weeks although benefits of both gradually decreased. The advantage of rifaximin remained. As noted, the NNT is at the borderline of clinical effectiveness.

2. Rifaximin (*Xifaxan*; Salix Pharmaceuticals) is a semi-synthetic rafamycin-based antibiotic. It is poorly absorbed (< 4%) In addition to treatment for traveler's diarrhea, it has been used to treat hepatic encephalopathy, for which it is approved by the FDA in 1998.

The company is seeking FDA approval for treatment of IBS, which requires 2 valid RCTs showing acceptable efficacy and safety.

Use now would be off-label. However, the drug has been used for years for other indications. It may be worth a try in a troubled patient, after fully informing her of benefits and risks, and allowing her to choose..

I do not know the cost of the drug.

KIDNEY DISEASE

Even Small Amounts of Pre-Existing Albuminuria Should Be A Red Flag

1-3 PROTEINURIA AND RISK OF ACUTE KIDNEY INJURY

A study of nearly one million adults published in this issue of Lancet[1] showed an independent association between estimated glomerular filtration rate (**eGFR**), proteinuria and incidence of acute kidney injury. It provided evidence that the risks of progression to end-stage kidney disease and death associated with acute kidney injury vary with proteinuria as well as eGFR.

Patients with eGFR of 60 mL/min per 1.73 m^2 and proteinuria (urine dipstick trace to 1+; mainly albumen) have 2.5 times the risk of hospital admission with acute kidney injury as do those with no proteinuria. Risk increased to 4.4 times with heavy proteinuria (dipstick proteinuria > 2+).

This confirms and expands reports suggesting that both eGFR and proteinuria are potent risk factors for subsequent acute kidney injury.

The "Atherosclerosis Risk in Communities" a population-based cohort study (2010) reported that even high-normal albuminuria increased risk for subsequent hospital admission for acute kidney injury independently of known risk factors such as eGFR and comorbid conditions.

Acute kidney injury is a growing public health issue. Admissions to hospital are now nearly as common as admissions for stroke. Some cases of acute kidney injury might be iatrogenic and preventable. In patients who are critically ill, drug-induced nephrotoxicity accounts for nearly a fifth of cases of acute kidney injury.

Contrast-induced nephropathy is well described and potentially avoidable. Among hospital admissions with acute kidney injury the frequency of antecedent intravenous contrast has increased over the past decade. Many procedures involving contrast administration are elective. More accurate identification of high risk patients might allow timely implementation of preventive measures. Although serum creatinine is commonly checked before a contrast load, few think of a urine dipstick.

Preventing kidney injury is paramount because we have little treatment to offer.

Acute kidney injury should be recognized as a potent predictor for long-term morbidity and mortality. Even small amounts of pre-existing albuminuria should be a red flag when assessing kidney-risk profile.

Urinary dipstick is cheap, simple, and widely available. It might be a start to reversing the world-wide trends in acute kidney injury, a common and deadly disease.

Lancet, December 18/25, 2010; 376: 2046-47 "Comment" first author Morgan Grams, Johns Hopkins School of Medicine, Baltimore MD

1 Glomerular Filtration Rate, Proteinuria, and the Incidence and Consequences of Acute Kidney Injury Lancer December 25, 2096-2103 (See full abstract)

I abstracted this article because detection of proteinuria by dipstick is simple, inexpensive, available, and almost instantaneous.

Detecting a decrease in kidney function (by both dipstick and eGFR) is important before subjecting a patient to drugs and procedures potentially harmful to the kidney. It may lead to substitution of a potential kidney-damaging drug by a less damaging drug.

Patients undergoing extensive surgical procedures (especially cardiac procedures) may develop impaired kidney function. If kidney function is impaired before surgery, the risk is magnified.

OBESITY

"Both Can Be Prevented Through Lifestyle Modifications"

2-4 IMPACT OF OBESITY AND KNEE ARTHRITIS ON MORTALITY AND MORBIDITY IN OLDER AMERICANS

The obesity epidemic and longer life expectancy have contributed to the high incidence of knee osteoarthritis (**KA**) in older Americans. Obesity and KA are among the most common comorbid condition in this age group.

Both KA and obesity can be prevented through lifestyle modifications.

This study assessed the longitudinal effect of obesity and KA on the remaining duration and quality of life in a population with highest burden of both conditions--persons age 50 to 84. Used a model to estimate quality-adjusted life-years (**Q-A-L-Y**) lost in the U.S. populating age 50 to 84 with obesity, or symptomatic KA, or both, over the remaining life-span.

The model summarizes the 1 million unique person-histories to provide stable estimates of duration and quality of life.

Population description (estimated) ages 54-80

A. Total population	85 966 000:
B. Obese	31 615 000 (36%)

Obesity; no KA 28 742 000 (33%)

Obesity and KA 2 871 000 (3.3%)

C. KA 5 674 000 (6.6%)

KA; no obesity 2 802 000 (3.3%)

Ka and obesity 2 871 000 (3.3%)

(Thus, over 1/3 of the U.S. population age 54-80 is obese. One in 16 has KA. And half of all KA is associated with obesity.)

Per person Q-A--L-Y lost:		Total quality-years lost
Obesity alone	2.4	80 804 000
KA alone	1.8	15 259 000
KA and obesity	3.5	

(Thus, on average, every person with obesity and KA loses over 3 quality-adjusted years of life.)

Symptomatic KA and obesity affect Q-A-L-Y loss through different mechanisms. Obesity is an independent risk factor for mortality, diabetes, coronary heart disease and other comorbid conditions that reduce survival. It reduces both the quality and quantity of life.

Symptomatic KA does not directly affect mortality, but considerably reduces Q-O-L, thereby diminishing quality-adjusted life expectancy.

With millions of Q-A- L-Y at stake, and the incidence of KA and obesity increasing, the potential public health effects of successful intervention to prevent these conditions is substantial.

These are estimates,, but, I think they have validity. The effect on public health is enormous. The costs to society, including cost of surgery, are huge.

I wish we had an answer.

Prevention Of CHD Should Start At An Early Age

4-1 ADOLESCENT BMI TRAJECTORY AND RISK OF DIABETES VERSUS CORONARY DISEASE

Obesity in adulthood is a risk factor for type-2 diabetes (**DM-2)** and coronary heart disease (**CHD**). It is not clear whether a long history of overweight, starting early in life, poses an additional risk.

The trajectory of weight and height from birth to adolescence is well known. The progression of body index (BMI; kg body weight divided by height in meters squared; kg/m^2) from adolescence into adulthood is less well described. Obese children have high likelihood of obesity in adulthood. Childhood obesity is associated with classic CVD risk factors as is adult obesity.

The study followed over 37 000 healthy young men whose BMI was measured in adolescence and repeatedly in early adulthood in order to identify incident cases of DM-2 and CHD.

All males eligible for the Israeli army are examined at age 17. Height, weight and BMI are determined. All remaining in the army after age 25 are examined every 3 to 5 years. This study included 37 674 male career army personnel. None had known DM-2 or CHD at baseline.

Follow-up and outcome: Participants were followed prospectively from the time of their first army examination at about 25 years of age. Measured height and weight and calculated BMI at age 17 (adolescence) were tracked retrospectively.

BMI and incidence of disease:

Diabetes:

A total of 1173 cases of DM-2 were diagnosed between ages 25 and 45. (Young adulthood). After adjustment for multiple possible confounders, adolescent BMI was predictive of incident diabetes, with a significantly increased risk observed at age 17 in the three highest BMI deciles (22.8. 24.1 and 27.6). Hazard ratio of the highest 3 deciles vs the lowest deciles was 2.76. The risk of diabetes increased by 9.8% for each 1 BMI unit.

Only BMI in adulthood was significantly associated with increased risk of diabetes.

(By the investigator's analysis, this was because individuals with high BMI in adolescence

were very likely to maintain high BMI in adulthood. If an individual with a high BMI in adolescence controlled weight and maintained a lower BMI in adulthood, the risk of DM-2 decreased. . The high BMI in adulthood was the reason for the high incidence of DM-2 in adulthood. Ed.)

CHD:

During a mean of 17 years, 327 cases of angiographic-proven CHD occurred.

The risk of CHD increased by 12% for each 1 BMI unit increase in adolescent BMI.

Both BMI in adolescence and adulthood were significantly and independently associated with risk for CHD. Adolescent BMI remained a risk factor for CHD that was independent of adult BMI.

Diabetes is influenced mainly by recent BMI in adulthood and weight gain whereas, for CHD,

both elevated BMI in adolescence and recent BMI in adulthood are independent risk factors. The natural history of CHD (in contrast with that of diabetes) is probably the consequence of gradual increasing atherosclerosis during adolescence and early adulthood that leads to clinically important disease in midlife.

It is noteworthy that these conclusions were deduced from adolescent BMI values that are well within the range of normal (22.8 and 24.1).

These conclusions highlight the clinical importance of considering BMI history when assessing
the risk of CHD vs the risk of diabetes in overweight or obese young men.

An elevated BMI in adolescence predicts CHD in early adulthood independently of the BMI in adulthood. The upper decile of adolescent BMI is related to seven times the risk of CHD as the lowest deciles.

These results may be explained by the fact that diabetes represents a more functional patho-mechanism than CHD, which relies on anatomical changes (atherosclerosis). Even clinically established diabetes is readily reversible in response to changes in lifestyle interventions, whereas atherosclerosis is responsive to diet interventions only if the intervention takes place before the “clinical horizon” of the disease is reached.

Conclusion: BMI in adolescence is an independent predictor of CHD in young adulthood even when it is well within what is now defined as the normal range of BMI. (Atherosclerosis begins at an early age.) Incident diabetes was mainly due to high BMI in adulthood.

Abstracting this study was a challenge. I think it is important for public health. Atherosclerosis begins at an early age. Prevention should start at an early age.

Adolescent BMI-adult BMI	*Risk of DM-2*	*Risk of CHD*
High-high	*Highest*	*Highest*
High-low	*Low*	*Still high*
Low-high	*High*	*Not as high*
Low-low	*Lowest*	*Lowest*

PHYSICIAN BIAS

Recommendations Should Reflect The Patient's Value System In The Light Of The Physician's Knowledge.

4-7 RECONCILING PHYSICIAN BIAS AND RECOMMENDATIONS

In this era of patient-centered care, some argue that physicians should refrain from advising patients or recommending a treatment course, and instead should neutrally present all the options and leave the final decision making exclusively to the patient.

The other option is, in a strong physician-patient relationship, physicians should use their knowledge to make recommendations to help patients make better-informed choices about therapy. Patients may be the ultimate deciders of what treatment to initiate, but they need physician experience and guidance to make the best choice.

A study in this issue of Archives[1] reports that physicians may make choices for patients, which differ from the choices they would make for themselves. Patients often place emphasis on decisions maximizing length of life. Physicians often emphasize quality of life. The weight given to a potential preventable death vs life with a serious lifelong disability may differ considerably depending on whether one is the prescriber or the recipient of the treatment.

Physicians may have a negative emotional reaction to the potential of serious long lasting adverse outcomes that some might view as being worse than death.

These editorialists argue that the cognitive biases expressed by physicians when thinking clinically for their patients are not less, but simply different, from their biases when thinking of themselves in the patient's role. Physicians may have a tendency to favor prolongation of life when making recommendations for their patients, but place more emphasis on quality-of-life when making decisions for themselves.

Given that physicians are human beings and subject to biases in their decision making and recommendations, how can they help their patients make the best possible decisions regarding their treatment?

Physicians must be attuned to the unique values of the patient. If the physician in that role tends to maximize length-of-life concerns and minimize risk of suffering this is fine as long as the patient shares these principles. But a healthy patient -physician relationship should allow the opportunity for the physician to explore the length-of-life and quality-of-life concerns of the patient as well as which complications are acceptable to the patient and which are not.

When making recommendations. physicians should try to fully integrate the values and concerns of each patient, and to carefully present the benefits and risks of treatment options. If gaps exist between what the doctor would do if he were in the patient's position and what he is recommending for the patient, it is important for the physician to reflect on this disparity and evaluate potential cognitive biases.

As long as the recommendations reflect the patient's value system in light of the physician's knowledge, it is relatively safe to proceed with recommendations.

Archives Internal Medicine April 11, 2011; 171: 634-35 "Commentary", first author Eric Shaban, University of Rochester, Rochester, NY

1 "Physician's Recommend Different Treatments For Patients Than They Would Choose For Themselves." Archives Internal Medicine April 11, 2011; 171: 630-34, first author Peter A Ubel, Duke University, Durham NC

I believe that many patients still leave judgments up to their doctors, trusting their advice and beneficence. I believe that doctors can gently guide patients to make reasonable choices.

Differences may be more acute at the end of the patient's life, especially when surrogates are making the decisions.

At the end, when the life loses all meaning and dignity, physicians can help surrogates to abandon "Life at all costs" and recognize that death is a necessary part of life. And help the patient to make a peaceful transition.

With the help of Hospice, physicians can help surrogates of loved ones who are at the end of life to be more comfortable and peaceful, while discontinuing the many unhelpful drugs these patients receive.

POLYPILL

"Potentially Highly Cost-Effective"

6-4 AN INTERNATIONAL RANDOMIZED PLACEBO-CONTROLLED TRIAL OF A FOUR COMPONENT COMBINATION PILL ("POLYPILL") IN PERSONS WITH RAISED CARDIOVASCULAR RISK.

In 2000, the World Health Organization and the Welcome Trust convened a meeting of experts to discuss evidence-based and affordable interventions for non-communicable diseases. A major impetus was the potential of a fixed-dose combination pill containing low doses of aspirin, a statin drug, and two BP-lowering drugs. The use of one pill daily containing all components would reduce cost and increase compliance.

In 2002, the WHO outlined the substantial potential public-health benefits and cost-effectiveness of such a pill, which was expected to substantially reduce cardiovascular risk in persons with cardiovascular disease.

This trial assessed the short-term efficacy and adverse effects of the polypill among people at raised risk of CVD. It was conducted in 7 countries 2008-2009. All subjects (n = 378; 13 subjects in the US; age range 50-70) had increased risk over 5-years determined by the Framingham risk function.

Randomized to low daily doses of 4 drugs:

1) Aspirin 75 mg
   Lisinopril 10 mg
   Hydrochlorothiazide 12.5 mg
   Simvastatin 20 mg, or
2) Placebo

Followed participants periodically for 12 weeks.

Expected reductions in CVD risk were estimated using data from systematic reviews, which have shown that each medication class confers approximately similar proportional reductions in cause-specific outcomes across a wide range of patient populations.

There was a wide range of baseline systolic BP (**SBP**) and LDL-cholesterol levels; 33% were regarded as hypertensive, 52% as pre-hypertensive, and 14% as normal ; 22% of participants had a 5.0-7.5% 5-year risk of CVD; 3% had a risk over 20%.

Over the 12-week follow-up, reductions were on average:

	Baseline	12-week change
SBP	134	-9,9
LDL-c	140	-31

Tolerance and adverse effects:

	Polypill	Placebo
Discontinued treatment	23%	18%
Reported adverse effects	58%	42%

Most adverse effects in the polypill group were attributed to the well-known adverse effects of aspirin—gastric irritation and bleeding, and to the ACE inhibitor—cough, headache, dizziness, and hypotension.

Predicted effects: One would expect a 60% reduction in CVD risk and a 50% increase in extra-cranial bleeding. (The adverse effects of aspirin balanced out the beneficial effects of BP-lowering.) In a patient group at a risk similar to the average in this trial, one would expect, over 5 years, about 1 in 18 would benefit in terms of avoiding a major event, largely due to SBP and LDL-c reduction. Among untreated patients with established CVD, the absolute benefit would be higher.

Most adverse effects, including virtually all major ones, were due to aspirin, which provided modest benefits. Even among patients with moderately elevated risk, the absolute benefit of aspirin was small.

Trials showing hard CVD end-points (eg, myocardial infarction and CVD death) would take years to complete.

Most all the benefits in the trial were due to BP and cholesterol lowering.

Conclusion: Over 12 weeks, the polypill achieved sizable reductions in SBP and LDL-cholesterol. It caused adverse effects in 1 of 6 people. The halving of predicted CVD risks was modestly lower than previous estimates, and the adverse effects modestly higher. Substantial benefit would be expected among patients at high risk.

The polypill principle is fascinating. It was first proposed by Wald and Law "A Strategy to Reduce Cardiovascular Risk by More than 80%" BMJ June 28, 2003; 326: 1419-23 (See www.practicalpointers.org June 2003 for an abstract.)

The original polypill consisted of low doses of 6 drugs: simvastatin, hydrochlorothiazide, atenolol, enalapril, folic acid and aspirin. The pill was to be given to all persons over age 55 without pre- or post-testing.

In view of advances in drug efficacy and knowledge about adverse effects, most of the drugs have been changed;

The present article suggests that the adverse effects of aspirin balance out the beneficial effects. Thus, an updated pill would omit aspirin. It would contain a statin, (eg simvastatin 20 mg) and 2 antihypertensive drugs. Some authorities would prefer a calcium blocker, instead of an ACE inhibitor, in patients over age 50, and chlorthalidone instead of hydrochlorothiazide. An updated pill would then contain: Simvastatin 20 mg, amlodipine 2.5 mg, and chlorthalidone 12.5 mg. All are available as generics. With a little trouble, the combination could be obtained at a modest cost.

Present "normal" (ie, target) BP and LDL-c levels are arbitrary. Many patients with levels below normal will benefit from further reductions in BP or LDL-c. And many will benefit by lowering a high level to a level still above target. The extent of the benefit depends on baseline risk. Lowering population SBP from 140 to 130 will benefit more (in absolute terms) than lowering it from 130 to 120.

Should primary care clinicians in the US ever prescribe the pill?

For patients who are compliant, but have limited resources and difficulty accessing medical care, I believe prescribing a polypill would be justified. It would still require some pre-testing and some post-testing.

I believe the principle of treating only patients with "abnormal" target levels will gradually be relaxed.

SMOKING

"There Are Few Healthcare Interventions More Impactful Than Helping Smokers Quit"

4-2 SMOKING CESSATION INTERVENTIONS: A Primer for Physicians

A suggested approach to cessation:

A. Follow the 5 A's (See the full abstract)

Set a quit date

Refer to a smoking cessation program or telephone quit line (1-800-QUITNOW)

B. Initiating drug treatment:

On the quit date, begin nicotine replacement therapy using a long-acting nicotine patch, approximating the current daily nicotine intake for 8 weeks. (Eg, a patch delivering 21 mg for a patient smoking a pack a day). Consider adding short-acting nicotine therapy (gum, lozenges, or inhalers) for acute craving, not to exceed an additional 12 mg/day of nicotine. Then taper the patch dose over a period of 4 weeks.

C. Alternative drug treatment (1):

Begin sustained release bupropion 1 to 2 weeks before the target quit date, using 150 mg every morning for 3 days, and then 150 mg twice a day for 7 to 12 weeks.

D. Alternative drug treatment (2):

Begin varenicline 1 week before target quit date at 0.5 mg twice daily for 4 days. Then 1 mg twice daily for 3 to 6 months.

Practical Pointers has abstracted a number of articles dealing with smoking cessation in the past. I found this article helpful, giving up-to-date information.

Please read the full abstract for more details.

If your patient is a smoker, ask if he is ready to quit every time you see him in consultation. If he says he does not want to stop, ask again later. Don't give up. We don't give up trying to control BP and weight.

Which treatment schedule to start? This would depend on the patient's individual choice.

Cost ; My pharmacy quotes:

Nicotine is available over the counter without a prescription

Varenicline 1 mg twice daily costs $182 for a 30 day supply

Bupropion sustained release is generic, but cost is high: $75 for a month's supply

STROKE

Immediate Treatment Is Urgent; Application Of Appropriate Treatment Is Often Low.

5-2 MEDICAL TREATMENT IN ACUTE AND LONG-TERM SECONDARY PREVENTION AFTER TRANSIENT ISCHEMIC ATTACK AND ISCHEMIC STROKE.

Although primary prevention is most important, secondary prevention is essential. Recurrent strokes are common, more severe than first strokes, and are more likely to cause dementia.

This review considers the evidence that led to this improvement in outcome. It is confined to the medical treatments that should be considered for most patients with TIA or IS.

Acute secondary prevention:

Secondary prevention should be started urgently after a TIA or minor stroke. A meta-analysis reported that stroke risk is 3.1% at 2 days and 5.2% at 7 days.

Acute treatment after TIA or minor stroke:

Urgent treatment within 1 day improves prognosis. A delay in treatment of 20 days was associated with a 10% risk of stroke vs 2% when treatment was started at day one.

Early administration of aspirin is beneficial. But guidelines still recommend aspirin + dipyridamole (*Aggrenox*) or clopidogril as first-line treatment. Clopidogril + aspirin is more beneficial than aspirin alone, but at increased risk of bleeding.

Antihypertensive drugs:

BP often rises shortly after a TIA or stroke. It tends to fall spontaneously during the first few days. Falling cerebral perfusion is less likely to be a concern after a TIA or minor stroke. Many clinicians start BP therapy immediately. It is not associated with a higher risk of stroke

Long-term secondary prevention:

Antiplatelet; anticoagulant

Appropriate use of anti-platelet drugs and anti-coagulants depends on whether the underlying cause is cardio-embolic or presumed arterial origin.

Arterial origin TIA or stroke

Aspirin is recommended for secondary prevention when the cause is arterial.

Guidelines still recommend aspirin + dipyridamole (*Aggrenox*) or clopidogril as first-line treatment. Vitamin K antagonists (eg. warfarin) are *not* recommended. Use is associated with increased intracranial hemorrhage.

Cerebral ischemia of cardiac origin:

About 20% of all TIA and ischemic stroke have a cardiac origin, most commonly with atrial fibrillation. (**AF**) . In patients with a recent TIA or ischemic stroke of cardiac origin, vitamin K antagonists (eg, warfarin) are preferred. Aspirin is of some value in patients who are ineligible for warfarin. Aspirin + clopidogril is *not* as effective as warfarin.

A trial of the direct thrombin inhibitor dabigatran 150 mg daily found fewer ischemic events with the same risk of hemorrhage as warfarin. A trial of a factor Xa inhibitor apixaban vs aspirin found a relative risk of primary outcome events of 0.45. Current guidelines still recommend warfarin as standard treatment in patients with AF. Long-term safety of the newer anticoagulants and their costs require further study.

Lipid modification

Statin drugs are effective. A reduction in LDL-cholesterol to 70 mg/dL was associatedwith a 28% greater reduction compared with a reduction to 100.

Antihypertensive drugs:

Hypertension (especially systolic) is the most important modifiable risk factor for stroke prevention, particularly in elderly people. A meta-analysis showed that reductions in BP lowered risk of recurrent stroke by 26%. A larger reduction was associated with greater benefit. Current guidelines recommend treatment with BP-lowering drugs in most patients with a history of TIA or stroke.

Potential long-term benefit of aggressive multi-risk factor control:

If one uses the observed treatment effect from randomized trials and assumes that the relative effects of each treatment are independent of the others, treatment of all major risk factors is estimated to reduce risk of recurrent stroke by 80%.

Conclusion: Secondary treatment with antiplatelet agents, antihypertensives, statins, and anticoagulation, and carotid endarterectomy as appropriate, should be initiated urgently after TIA or minor stroke. The risk of recurrent stroke is high. For long-term secondary prevention, most

guidelines recommend aspirin plus dipyridamole or clopidogril for cerebral ischemia of arterial origin. For cardiac origin, factor Xa inhibitors and thrombin inhibitors are challenging the current standard of vitamin K antagonists. Lipid-lowering and antihypertensive treatments are warranted after both types of cerebral ischemia (arterial and cardiac).

This is the UK view. It is straightforward and simple. The article did not elaborate on carotid endarterectomy.

All primary care clinicians are aware of these interventions. The challenge is to apply them promptly and long-term. The interventions apply to primary prevention as well.

See the full abstract.

SURROGATE DECISION MAKING

3-3 THE EFFECTS ON SURROGATES OF MAKING TREATMENT DECISIONS FOR OTHERS; Systematic Review

Many adult patients near the end of life cannot make their own treatment decisions. Standard practice relies on surrogates to make decisions for them, typically in consultation with the patient's physician.

If making treatment decisions has a negative psychological effect, it might impair a surrogate's ability to protect patients who lack decision-making capacity, and would represent a harm to surrogates. In addition, it might conflict with the preferences of patients who do not want to be a burden to their family.

This review assessed the effects on surrogates of making treatment decisions for adults who cannot make their own decisions.

Literature search identified 5221 possibly relevant studies. Of these, 40 met inclusion criteria.

Of these 40 studies (n = 2854 surrogates), 29 used qualitative data and 11 used quantitative data. More than half of the surrogates were family members of the patients. Most were surveyed months to years after making the treatment decisions, the majority of which were end-of-life decisions (choosing to initiate, withhold, continue, or withdraw life-sustaining treatment).

The most common reported stressors::

Unsure of the patient's wishes

Uncertain prognosis

Discomfort with the hospital environment

Poor communication with the clinician

Insufficient time

Sense of sole responsibility

Uncertainty or guilt over decisions

Making treatment decisions for incapacitated loved ones places an emotional burden on at least one third of surrogates.

Being confident of which treatment the patient would want has an important protective effect for surrogates.

Methods for making treatment decisions would ideally promote at least 3 goals:

1) Identifying treatments that are consistent with the patient's preferences.

2) Respecting patient's preferences regarding how treatment decisions are made.

3) Protecting the patient's family and loved ones.

This is an important aspect of primary care medicine. Read the full abstract.

Primary care clinicians should encourage elderly patients to think about advanced directives, living wills, and a durable power of attorney. It is important to get the whole family on the same page. The elderly patient should leave no uncertainty. Nothing splits a family more than disagreement about terminal care. Instructions should not only be in writing, but also freely discussed when families get together for holidays.

I believe that many elderly persons are now considering death a normal and necessary part of living, not a reason for dread. They seek a "good death". They realize that some states of incapacity are worse than death.

If I remember accurately, one proposed change in the new health care law allowed payment to primary care clinicians for counseling elders and families about the importance of planning for terminal care. Some detractors termed the effort "Pulling the plug on Grandma".

TELEVISION VIEWING

Prolonged Daily TV Viewing Was Consistently Associated With Increased Risk

6-3 TELEVISION VIEWING AND RISK OF TYPE-2 DIABETES, CARDIOVASCULAR DISEASE, AND ALL-CAUSE MORTALITY

On average, 40% of daily free time (about 4 hours) is occupied by TV viewing.

TV viewing displaces more active energy expenditure.

This meta-analysis summarized all published cohort studies on the incidence of type-2 diabetes (**DM-2**), non-fatal and fatal cardiovascular disease (**CVD**), and all-cause mortality related to the amount of daily TV viewing.

A systematic search (1970-2011) found 8 relevant studies (Europe, Australia, and the US). Some studies reported outcomes for more than one endpoint (eg, DM-2 and CVD). All were prospective. The study population was healthy at baseline.

Total numbers in the 8 studies:

	Individuals	Person-years	Cases	Mean years
DM-2	175 938	1 100 000	6428	8.5
CVD (fatal & non-fatal	34 253	-	1052	10.4
All-cause mortality	26 509	202 353	1879	6.8

(Adjusted for multiple confounding factors)

Adjusted relative risk (RR) per each 2-hours of TV viewing per day:

	RR (pooled)
DM-2	1.20
CVD	1.15
All-cause mortality	1.13

Each 2-hours of daily TV viewing was associated with 176 cases of DM-2; 38 cases of CVD; and 104 cases of all-cause mortality per year.

There was a linear dose response for each outcome.

Conclusion: Prolonged daily TV viewing was consistently associated with increased risk of DM-2, CVD, and all-cause mortality

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We live in a sedentary society. We work at desks, at computers, study, and read. All non-physical activities. All could be added to judge total adverse effects of sedation.

Most of us have to make conscious efforts to increases physical activity. Many, including primary care physicians, fail to do so. Of course, primary care clinicians should encourage continuing physical fitness as part of the healthy lifestyle. They must first act as a role model and maintain fitness themselves.

VITAMIN D

IOM Recommendations for The General Healthy Population

1-1 THE INSTITUTE OF MEDICINE REPORTS ON VITAMIN D AND CALCIUM

[Note: This is not the official communication from the IOM. I abstracted it from the JAMA February 2, 2011;305:454-56 "Medical News and Perspective" by Anna Slomski, JAMA Staff Editor]

The governments of U.S. and Canada recently charged a group of scientists (The Institute of Medicine [**IOM])** with updating the Dietary Reference Intake for vitamin D and calcium.

The committee reviewed 1000 studies on 25 health outcomes.

They also flatly declared that "the data just aren't there" to recommend that people consume *high* amounts of D and calcium.

Vitamin D:

They did recommend a higher D intake--a three-fold increase of some age groups--compared with levels set by the IOM in 1997:

1) Generally, to maintain bone health, 600 IU daily.
2) After age 70, 800 IU daily if the individual is not physically active and has significant declines in kidney function.

This new Recommended Daily Allowance (RDA) is a measure of nutrient intake that meets the needs of 97%% of the population. (In 1997, the recommendation was for 200 IU daily for persons up to age 50; 400 IU for those 51 to 79; and 600 IU over 70.)

The committee set the upper safe boundary to daily intake at 4000 IU of D. But this is not the amount people should aim for.

Although most North Americans get one third of their D requirement through skin synthesis, the committee took a "markedly cautious approach" in setting its new level for D based on sunlight exposure. Sunlight as a source of D is a problem because of the known risk of UV-induced skin cancers. But getting enough D from diet alone is problematic.

The claim that there is widespread D deficiency is based on the lack of consensus on how to define adequate serum levels of 25-OHD The committee defined deficiency as below a level of 12 ng/mL, and insufficiency as 12 to 19 ng/mL.

The committee thinks that 20 ng/mL meets the needs of almost all of the healthy population, and found no evidence that going higher confers additional benefit. Other prestigious foundational and societies set the lower normal limit at 30.

The committee set the upper limit of D at 4000 IU/d so there is no downside to individuals increasing their intake to 1000 IU daily.

There is evidence that higher serum levels of D at or above 40 ng/mL are associated with all-cause mortality, pancreatic cancer and prostate cancer. Above 10 000 IU/d, there is clear evidence of risk.

But even assuming the 20 ng/mL is the threshold for adequate serum levels of D, a significant portion of the U.S. population remains insufficient. NHANES in 2000-2004 found that 50% of black children and teenagers had levels of 25-OHD less than 15 ng/mL, as did 9% of all children. Of the teens tested, 61% had D insufficiency at levels of 15 to 19. In one study, serum levels 76% pregnant women at term were insufficient, (serum D less than 20), as were 81% of infants.

The committee declared an "urgent need" to standardize D assays, and develop consensus for recommended values.

In the last few years, there has been a dramatic increase in testing serum D levels as part of routine medical care. Physicians should judge the risk for low D in each individual, and assess whether they need testing.

The new IOM recommendations are for the general healthy population and do not pertain to people with medical conditions that can cause malabsorption of D and calcium.

In evaluating the purported role of D in preventing numerous diseases, the IOM committee said that there is a paucity of randomized clinical trials Observational studies provide conflicting evidence. This led to their conclusion that numerous links to outcomes, other than bone health, are best described as hypotheses of emerging interest.

Calcium:

The calcium requirement did not change appreciably. North Americans need from 700 to 1300 mg/d depending on age.

The committee set the safe upper boundary of daily calcium intake at 2000 to 3000 mg, but this is not the amount people should aim for.

Calcium from diet and supplements:

Most individuals can achieve the recommended amounts of calcium through diet alone. Some age 9 to 18 fall short of the recommended 1300 mg.

Many postmenopausal women are at risk of failing to consume the recommended 1200 mg through diet alone. But many who take calcium supplements are getting too much. "Many physicians have incorrectly interpreted women's total 1200 as the amount they should be getting in a supplement." Most people get at least 600 mg and up to 900 mg from their diet and are also taking a 1200 mg supplement. They may be beyond the 2000 mg safe upper limit.

The committee found that 5% of women older than 51 had an intake above the upper limit, putting them at risk for kidney stones and possibly cardiovascular disease.

I believe we can depend on some points:

1. *Many persons of all ages in the U.S. are D insufficient and require supplementation. This includes teens and pregnant women. Elderly persons, sedentary and living indoors in nursing homes, are especially prone to D insufficiency. Would it not be reasonable to treat them with 1000 IU of D daily on an empiric basic?*
2. *Don't depend on sunlight to produce enough D.*
3. *D supplements are safe up to 4000 IU daily. Do not aim for this amount.*
4. *We still do not know the lower normal level of serum 25-OHD. It may be 20 ng/mL or 30 ng/mL*
5. *Many teens fail to ingest the required calcium of 1300 g daily--this at a time when bones are maturing.*
6. *Some persons are taking too much calcium, some by over supplementation advised by their physician. Don't exceed 2000 mg daily.*
7. *The data on preventing of diseases other than bone is based on*

observational studies and remain a hypothesis of emerging interest.

8. For a normal healthy person:

For D: 600 IU daily; after age 70, 800 IU

For calcium: up to 1300 mg; no more than 2000 mg daily.

Fortunately, the benefit / harm-cost ratio of supplemental D is very high. Some pharmacies sell 1000 IU of D3 for 3 cents each.

This abstract focused mainly on normal requirements of healthy people.

For those who are insufficient or deficient, higher doses are required.

See the following abstract

1-2 VITAMIN D INSUFFICIENCY

Serum 25-hydroxy vitamin D (**D**; **25-OHD**) *deficiency*, below 10 ng/mL (25 mmol/L), has long been recognized as a medical condition. It is characterized by muscle weakness, bone pain and fragility fractures. D is critical for skeletal mineralization.

Low dietary intake of D coupled with negligible exposure to sunlight may cause levels to decline below 10 ng/mL.

An international workshop (2007) agreed that most of the world's populations is not getting sufficient D to maintain healthy bone mass and to minimize risk of fracture. It also agreed that D insufficiency decreases muscle strength and increases risk of falls.

Vitamin D *insufficiency*, variously described as 25-OHD 10 to 29, or 10 to 19 ng/mL without overt clinical symptoms, has recently become a concern. The average dietary intake of D (including supplements) in the US is 200 IU per day. Skin-derived synthesis of D is quite variable,

Whatever range is used, the estimated prevalence of D insufficiency is as high as 50% to 80% in the general population.

A 2007 meta-analysis of 29 trials of supplementation with both calcium and D and with calcium-alone suggested that daily supplementation with 1200 g calcium and 800 IU D reduced rates of fracture and modestly increased bone mineral density,

A 2009 Cochrane meta-analysis testing the effects of D supplements alone showed no significant reduction in risk of fractures. Combined calcium + D was marginally effective in reducing rate of fractures in the elderly as compared with no supplementation.

Observational studies have shown significant associations between levels of 25-OHD below 20 ng/mL and increased risk of metabolic, neoplastic, and immune disorders, multiple sclerosis, atherosclerosis, diabetes, and cardiovascular disease.

However, there is not enough data from large randomized trials to assess whether D supplements reduce risk of chronic disease other than osteoporosis.

Toxicity from D is rare. If it occurs, it in usually the form of acute hypercalcemia, which usually result from doses that exceed 10 000 IU daily. Associated serum levels of 25-OHD are above 150 ng/mL. The Institute of Medicine (2009) set the tolerable upper level of D at 4000 IU daily.

In 2010 the International Osteoporosis Society, based on observational data, recommended a target serum level of 30 ng/mL in all elderly persons, and that a daily dose of 2000 IU may be necessary to attain that level.

In contrast, the Institute of Medicine suggested a 25-OHD level of 20 would protect 97.5% of the population against fractures and falls. The IOM recommended a dose of 600 IU daily for postmenopausal women who are not at high risk of fracture and falls, and 800 IU for persons who are over age 70.

How should primary care clinicians respond to these 2 articles? What should we believe?

Vitamin D (is it really a "vitamin"?) remains as the only vitamin deficiency which is wide-spread in developed countries. The average daily intake is low.

After all these years, there is much we still do not know. We can't agree on the biochemical definition of insufficiency. This should be settled. We can believe that insufficiency is common. We cannot rely on sunlight to produce the optimal amount. Supplements must be added. We cannot agree on the dose of supplementation. For bone health, calcium supplementation is also required. I believe, in general, modest doses (eg, 1000 mg daily) are sufficient.

Except for effects on bone metabolism, the benefits of supplementation are not known. We may be overtreating those with serum 25-OHD levels 20 to 30. But D at usual doses is non-toxic.

It is inexpensive .

I believe primary care clinicians should err on the side of advising supplements: 1000 and 1000 might be a good rule of thumb.

There are individuals for whom empiric supplementation is a reasonable approach--elderly persons living indoors; teen-agers, especially girls (they should enter menopause with a strong bone structure); and women entering the menopause, when loss of estrogen deficiency leads to rapid bone loss.

We do not necessarily have to await results of serum levels.

The dose of calcium should be modest-- not over 2 grams a day.

We await large long-term randomized controlled trials to determine if D has any effect on other disorders.

The Evidence For Cancer Prevention Is Inconsistent And Inconclusive.

3-6 VITAMIN D AND PREVENTION OF CANCER-- Ready for Prime Time?

The Institute of Medicine (**IOM**) is charged with determining the population needs for vitamin D (**D**) in North America. In 2011 a committee of the IOM published an updated Dietary Reference Intake for Vitamin D after reviewing the evidence linking D with skeletal and non--skeletal health outcomes.

The IOM concluded that D plays an important role in bone health and that the evidence provides a sound basis for determining the population's needs for it.

Based on D's importance to bone health, the recommended daily allowances (RDA) are 600 IU for persons age 1 to 70, and 800 IU per day for those over 70. This corresponds to a serum level of 25OHD of at least 20 ng/mL.

Because of the wide variation in sun exposure and skin synthesis of D, and the known risks of skin cancer, the recommendation was made under the assumption that skin exposure would be minimal.

The IOM also concluded that the prevalence of D inadequacy in North America has been overstated. Most North Americans have serum levels above 20, which is adequate for bone health in at least 95% of the population.

Four outcomes beyond bone health (cancer, cardiovascular, diabetes, and autoimmune disorders) were also considered. The IOM found that the evidence of them was inconsistent and inconclusive.

The committee's comprehensive review of the evidence of D's role in preventing cancer concluded that the research is inconsistent and does not establish a cause-effect relationship.

Other recent reviews have reached similar conclusions. No large scale randomized controlled trial has been completed regarding the effect of D on cancer as the primary prespecified outcome. Most evidence thus far is derived from laboratory studies, ecological correlations, and observational investigations of 25OHD levels. in association with cancer outcomes. Association studies have important limitations. Low 25OHD levels are also linked with confounding factors related to high cancer risk: Obesity (D becomes sequestered in adipose tissue), lack of physical activity (correlated with less time outdoors and less solar exposure), dark skin pigmentation (less synthesis of D), and diet or supplementation practices. Reverse causation biases may also occur if poor health reduces participation in outdoor activities and limited sun exposure lowers D levels.

Association cannot prove causation.

Many micronutrients that seemed promising in observational studies were not found to reduce cancer risk in randomized trials. (Eg, beta carotene, vitamins C and E, and folic acid.) Some were found to cause harm at high doses.

The theory that D can help prevent cancer is biologically plausible. Studies in cell culture and experimental models suggest that calcitriol promotes cell differentiation, inhibits cancer cell proliferation, and exhibits anti-inflammatory and anti-angiogenic properties. This suggests, but does not prove a role for D in cancer prevention.

Randomized trials are sparse. Three randomized trials have assessed the occurrence of cancer mortality as secondary outcomes. Results were null.

1) Oxfords UK: Of 2686 men and women given D or placebo. More cancers occurred in the D group. (188 vs 173; RR = 1.08)
2) Nebraska USA : Of 1179 postmenopausal women, those given D were less likely to develop cancer (13 vs 17; RR = 0.74)
3) Woman's Health Initiative USA: Of 32 282, subjects, those receiving D were less likely to develop cancer. (1634 vs 1655; RR = 0.98)

None was statistically significant.

Breast cancer: Three observational studies were inconclusive. The large Women's Health Initiative, which assessed breast cancer as a separate secondary outcome, found the D had no significant effect.

Colorectal cancer: Observational studies generally support an inverse relationship. In a meta-analysis of 5 prospective studies, subjects with a 25OHD level of 33 ng/mL had about half the risk of colorectal cancer as those with levels of 12 ng/mL. The European Prospective Investigation into Cancer and Nutrition found a similar strong inverse relationship. A study from Japan reported benefit only for rectal cancers. A British trial of D vs placebo and the Women's Health Initiative trial reported no benefit.

Prostate cancer: Eight of 12 nested case-control studies showed no association between baseline levels of 25OHD levels and risk.

Less common cancers: The large Colon Cancer Consortium Vitamin D Pooling Project of Rarer Cancers showed no evidence linking higher 25OHD levels with reduced risk of many cancers (endometrial, esophageal, gastric, pancreatic, kidney, ovary, and non-Hodgkin's lymphoma). Moreover the study reported an increased incidence of pancreatic cancer with 24OHD levels over 39 ng/mL. An increased incidence of esophageal cancer was also reported.

Despite biologic plausibility and widespread enthusiasm, the IOM found the evidence that D reduces cancer incidence and mortality of cancers was inconsistent and inconclusive.

NEJM April 14, 2011; 364: 1385-87 "Perspective", Editorial, first author JoAnn E Manson, Brigham and Women's Hospital, Harvard Medical School, Boston Mass. Dr. Manson is a member of the IOM Committee.

Recently, Practical Pointers has abstracted many articles about D --most suggesting a benefit. I hope this is the last until a large definitive randomized trial is published.

Is D going the way of "estrogens forever" and antioxidants?

In the past, many observational studies have overemphasized benefits of treatments. These are not fraudulent. It is the nature of observational studies, perhaps augmented by enthusiastic proponents of a new theory.

Meanwhile, what should the primary care clinician do abut D? I believe many individuals in the US are deficient. Older patients who are house-confined or in nursing homes are not exposed to sunlight. Their diets may be deficient in D. Growing children may not get enough D and calcium.

The benefit / harm-cost ratio of D remains high, Benefits may be substantial; harms and costs are nil.

Fortunately, in medicine the truth will out. It may take years or decades.

I hope D will survive.