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**INDEX and SYNOPSIS**

**JANUARY – JUNE 2012**

**PRACTICAL CLINICAL POINTS**

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**JAMA, NEJM, BMJ, LANCET**

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**ANNALS INTERNAL MEDICINE**

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**EDITED BY RICHARD T. JAMES JR. MD**

**400 AVINGER LANE, SUITE 203**

**DAVIDSON NC 28036 USA**

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**To request free monthly issues by e-mail attachment go to [Rjames6556@aol.com](mailto:Rjames6556@aol.com)**

This index-synopsis is a reference document based on articles abstracted from 6 flagship journals. January – June 2012. It provides a means of reviewing and recalling to memory, in an evening or two, practical clinical points of importance to primary care published during that time.

The numbers in the brackets refer to the abstract. For example, [6-3; DIABETES] refers to the sixth article abstracted in June. DIABETES refers to the MeSH under which the abstract appears.

This Index-Synopsis is divided into 5 parts:

- 1) “Practical Clinical Points”: A sentence or two 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 ALZHEIMER’S DISEASE to VITAMIN D, arranged alphabetically
- 3) The abstracts appear under each MESH. There may be several under a MeSH.
- 4) The citation is attached to each abstract
- 5) *Editorial Comments*”: linked to 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*.

Monthly issues for the past 10 years may be found on the website ([www.practicalpointers.org](http://www.practicalpointers.org)).

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

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

## **PRACTICAL CLINICAL POINTS JANUARY-JUNE 2012**

- [1-1; CARDIOVASCULAR DISEASE]** In contrast with the Framingham Risk Score, which estimates risk of CVD events over 10 years, the “Lifetime Risks of Cardiovascular Disease” estimates risk from middle age to old age. It uses total cholesterol; BP; smoking; and diabetes as risk markers. As the number and severity of the risk rose from optimal to two or more major factors present, risk of total atherosclerotic events rose stepwise from 15% to 47%. Deaths from CVD rose similarly.
- [1-2, BONE DENSITY TESTING]** Osteoporosis would develop in less than 10% of older postmenopausal women during screening intervals of 15 years for those with normal bone mineral density and mild osteopenia; 5 years for those with moderate osteopenia; and 1 year for those with advanced osteopenia. Screening often is performed more frequently without benefit and with increasing costs.
- [1-3; HYPERTENSION]** Initiating treatment of hypertension in octogenarians is beneficial in (modestly) lowering incidence of stroke, CVD mortality, and heart failure.
- [1-4; DYSLIPIDEMIA]** Should we screen for and treat dyslipidemia in select children and adolescents?
- [1-5; VITAMIN D]** The increase in requests for vitamin D serum measurements is “costly, confusing, and without merit”
- [2-1; COLONOSCOPY]** Colonoscopic removal of adenomas prevents death from colorectal cancer.
- [2-2; COLO-RECTAL CANCER]** Patients randomized to testing for occult blood by fecal immuno-chemical tests (FIT) detected similar colo-rectal cancers as colonoscopy. Patients were more likely to participate in screening with FIT. But more adenomas were detected by colonoscopy.
- [2-3; HORMONE REPLACEMENT THERAPY]** Hormone replacement therapy (estrogen + progesterone) has adverse effects: Breast cancer; venous thromboembolism; stroke; cholecystitis; and coronary heart disease. It is effective in reducing menopausal symptoms. It should be used in the lowest dose for the shortest time.
- [2-4; RHINO-SINUSITIS]** Amoxicillin treatment for 10 days offers little clinical benefit for patients with uncomplicated rhinosinusitis.
- [2-5; FAMILY HISTORY]** Adding a systematic family history enquiry to cardiovascular disease

risk assessment increased the numbers considered at high risk.

[3-1]; **CARDIOVASCULAR DISEASE]** The American Heart Association has announced a new strategy to improve cardiovascular health. The patterns of ideal CV health is present in most infants. But it is lost rapidly during childhood and adolescence. *Primordial prevention* differs from primary and secondary prevention. It prevents risk factors from developing in the first place, instead of waiting until they develop and then treating. Begin the usual healthy behavior at a very early age.

[3-2; **SITTING TIME]** Prolonged sitting is a risk factor for all-cause mortality, independent of physical activity.

[3-3; **HYPOTHYROIDISM]** Subclinical hypothyroidism occurs when the thyroid stimulation hormone (TSH) is high and the free thyroxin level (T4) is within normal limits. It is without obvious symptoms. It is a laboratory diagnosis. It is common in primary care practice when screening lab profiles are ordered frequently. Experts do not agree on whether screening is worthwhile. Treatment is recommended in patient with TSH levels of 10 mIU/L and over. No firm recommendations can be made for those with TSH 5 to 10. At present, clinicians must rely on their clinical judgment and well-meaning, but necessarily vague guidelines and expert opinion.

[3-4; **CHOLESTEROL]** Among high-risk patients treated with statin, levels of non-HDL-cholesterol were more strongly associated with risk of future CVD events than LDL-c and HDL-c.

[3-5; **ALZHEIMER'S DISEASE]** Donepezil and memantine for moderate to severe Alzheimer's disease: Two interpretations:

**A. Article conclusion:**

In patients with moderate or severe Alzheimer's disease, continuing treatment with donepezil was associated with cognitive benefit that exceeded the minimum clinically important difference and with significant functional benefit over the course of 12 months.

**B. Alternative conclusion (by the editor of Practical Pointers)**

In patients with moderate or severe Alzheimer's disease who were already taking D, continued treatment with D over the next year was associated with continuing increases in dementia and dependency, but not as rapidly as in those taking memantine or no drug.

**[4-1; PATIENT CARE] Putting patients first:**

**Know the patient as an individual**

**Tailor healthcare services to the individual**

**Ensure continuity of care and relationships**

**Enable active participation of patients in their care**

**[4-2; STATIN DRUGS] Should a 55-year old man with a total cholesterol of 250, who is otherwise well without any other risk factors, be treated with statins? The debate continues:**

**Yes: Statin therapy is a critical adjunct. Adverse effects are rare**

**No: Statins are not effective in improving length or quality of life when used for primary prevention.**

**[4-3; RED MEAT CONSUMPTION] Consumption of red meat is associated with increased risk of mortality.**

**[4-4; COFFEE DRINKING] Coffee consumption does not adversely affect health. There is an inverse association of coffee drinking with all-cause death.**

**[4-5; CARDIOVASCULAR DISEASE] Primary prevention of cardiovascular disease. Medicine must negotiate a precarious bargain. Primary prevention is a philosophical question just as it is a medical question.**

**[5-1; END OF LIFE CONVERSATION] At the end of life, patients and families need advice about what interventions are appropriate. Patient autonomy is not synonymous with endless choice. Shifting the burden to the patient or family is not patient-centered care.**

**[5-2 ANTIBIOTIC ASSOCIATED DIARRHEA] Probiotics are associated with lower risk for antibiotic-associated diarrhea.**

**[5-3 HYPERTHYROIDISM] Subclinical *hyper*-thyroidism is associated with increased risk of all-cause mortality, CHD mortality and atrial fibrillation**

**[5-4 HYPERTHYROIDISM] Subclinical *hyper*-thyroidism: When TSH is less than 0.10 mIU/L, treatment should be strongly considered.**

**5-5 CHOOSING WISELY] “Choosing wisely” A list of 16 DO and DO NOT recommendations to help primary care clinicians and patients make smart decisions about care.**

**[6-1 PATIENT CARE] An Alternative Health Outcome Paradigm. Ultimately, good medicine is**

**about doing the right thing for the patient. For patients with multiple diseases, severe disability, or limited life-expectancy, any accounting of how well we are succeeding in providing care must above all consider the patient's preferred outcomes.**

**Do the right thing for the patient—make health care more patient-centered.**

**[6-2 COLORECTAL CANCER] Colo-rectal cancer incidence and mortality were reduced by over 20% by screening flexible sigmoidoscopy. (Followed by colonoscopy if adenomas were found.) Benefits were limited to outcomes from distal cancer.**

**[6-3 DIABETES] Prediabetes: A High-Risk State For Diabetes Development. According to the ADA, up to 70% of individuals with PD will eventually develop DM--2. Risk predictors include: age; BMI; waist circumference; hypertension; family history; smoking; physical inactivity; blood levels of glucose at the high end of the PD range; and triglyceride, uric acid, and lipid levels. Lifestyle interventions and metformin therapy will reduce incidence.**

**[6-4 DIABETES] Guidelines are easing up on glycemic control in some patients with diabetes. The ADA released a report in April 2012 calling for a more patient-centered treatment approach that takes into account patient needs, preferences, and tolerances. The report noted that lowering HbA1c below 7.0% is still recommended in most patients. Less stringent goals, between 7.0% to 8.0%, are appropriate for patients with a history of severe hypoglycemia, limited life-expectancy, advanced complications, extensive co-morbid conditions, and those that have difficulty attaining the 7.0% goal despite intensive self-management, education, repeated consultations, and effective doses of glucose-lowering agents, including insulin.**

# **MEDICAL SUBJECT HEADINGS (MeSH)**

**JANUARY-JUNE 201**

**ALZHEIMER DISEASE**

**AMOXICILLIN**

**ANTIBIOTIC ASSOCIATED DIARRHEA**

**PATIENT CARE**

**BONE DENSITY TESTING**

**PREDIABETES**

**CARDIOVASCULAR DISEASE**

**RED MEAT CONSUMPTION**

**CHOLESTEROL**

**RHINO SINUSITIS**

**CHOOSING WISELY**

**COFFEE DRINKING**

**SCREENING**

**COLONOSCOPY**

**SITTING TIME**

**COLORECTAL CANCER**

**STATIN DRUGS**

**VITAMIN D**

**DIABETES**

**DONEPEZIL**

**DYSLIPIDEMIA**

**END OF LIFE CONVERSATION**

**FAMILY HISTORY**

**FECAL IMMUNOCHEMICAL TESTING**

**HORMONE REPLACEMENT THERAPY**

**HYPERTENSION**

**HYPERTHYROIDISM**

**HYPOTHYROIDISM**

# ABSTRACTS AND *EDITORIAL COMMENTS*

JANUARY-JUNE 2012

## ALZHEIMER DISEASE

### *Dementia And Dependency Relentlessly Continued*

### **3-5 DONEPEZIL AND MEMANTINE FOR MODERATE-TO SEVERE ALZHEIMERS DISEASE**

Guidelines advocate cholinesterase inhibitors (eg, donepezil [**D**]) for treatment of Alzheimer disease (**AD**). Some recommend discontinuation when AD becomes severe. The FDA has approved D for treatment of severe AD.

Memantine (**M**) has been reported to be effective in patients with moderate or severe AD.

There is limited evidence to guide the difficult decision regarding continuation of treatment when AD progresses. Continuing treatment is associated with adverse outcomes.

This study of AD patients, who were already taking D, asks whether continuation of D-alone, M-alone, M + D, or no drug therapy would be the superior treatment.

This double-blind, placebo-controlled trial entered 295 community dwelling patients (mean age 77) with moderate to severe AD and followed them for 52 weeks. All had been taking D for between 3 months and 5 years.

All had a baseline score between 5 and 13 (mean = 9) on the Mini-Mental State Examination (**MMSE**). Possible scores ranged from 0 to 30, with higher scores indicating better cognitive function. Score of 5 to 9 indicated severe AD; 10 to 13, moderate AD.

All also had a baseline caregiver score on The Bristol Activities of Daily Living Scale (**BADLS**) ranges from 0 to 60, with higher scores indicating greater impairment. Mean baseline score was 28.

Randomized to: 1) Continuation of D-alone; 2) M; alone; 3) D + M; or 4) No drug therapy. Placebos were added as needed to blind treatments.

Over one year, mean scores on the MMSE in all 4 groups relentlessly continued to deteriorate from a mean baseline score of 9:

	D-alone	M alone	D + M	No drug	
MMSE from 9 to	5.5	5.0	5.5	3.5	(Worsening)
BADLS from 28 to	35	36	34	41	(Worsening)

The primary outcome measure: The overall mean differences between drug and no drug across all visits ( weeks 6, 18, 30, and 52):

D alone +1.9 points on MMSE; - 3 points on BADLS

M-alone +1.2 points of MMSE; -1.5 points on BADLS

Both drugs showed better scores compared to no drug treatment, but both drugs were associated with a continuing decline in cognitive function and activities of daily living.

There was no clinically important difference between groups in behavioral and psychological symptoms.

“This double-blind, placebo –controlled trial involving community living patients with moderate or severe Alzheimer’s disease who were already receiving treatment with a cholinesterase inhibitor, showed that there was modest cognitive and functional benefit of continuing donepezil over the course of 12 months.”

There was no significant benefit from adding M to D.

The improvements in cognition and function associated with D and M were small relative to the overall size of the decline in cognition and functional status that was seen in all patients.

Conclusion: In patients with moderate or severe AD, continuing treatment with D was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over 12 months.

NEJM March 8, 2012; 366: 893-90 Original investigation, first author Robert Howard, Kings College, London.

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*This complex article was difficult to abstract.*

*Casual readers may miss the important outcomes.*

*I believe it stresses the wrong outcomes. Although D was “better” than the other interventions, cognitive function and difficulties with daily living progressed relentlessly over the year.*

*The authors did not stress this point. They stressed the difference between the 4 interventions and the advantages of D over the rest. This is not a valid clinical point for primary care.*

*Both D and M have a wide variety of adverse effects. Benefits, if any, are small. The benefit/harm-cost ratio is, in many patients, less than 1/1.*

*I believe these drugs have been over prescribed, overused. They may retard progressing of dementia to a small degree in those with beginning AD, but they are continued without benefit.*

*They are costly, especially if used for years.*

*Why are these drugs used so frequently? I believe because family members latch onto any intervention which promises some benefit and hope, no matter how small. And because drug companies advertise them so forcefully.*

## **ANTIBIOTIC ASSOCIATED DIARRHEA**

### ***Probiotics Are Associated With Lower Risk For AAD.***

#### **5-1 PROBIOTICS AND THE PREVENTION AND TREATMENT OF ANTIBIOTIC-ASSOCIATED DIARRHEA**

Antibiotics that disturb the gastrointestinal flora are associated with diarrhea, which can occur in up to 30% of patients. Symptoms may be mild and self-limiting, or severe (as with *Clostridium difficile* infection).

Probiotics may maintain or restore gut micro-ecology during or after antibiotic treatment.

This systematic review and meta-analysis evaluated and updated the available evidence on live probiotics on incidence of antibiotic-associated diarrhea (AAD).

Selected randomized controlled trials (RCT) that compared probiotics use as an adjunct to antibiotics vs. a concurrent control group. (As a supplement given with antibiotic at onset of treatment.)

The majority used *Lactobacillus* alone or in combination with other genera.

The primary outcome was the number of participants with diarrhea in each treatment group.

The quality of the trials was low. Questions about conflict of interest and bias remained.

Efficacy: 63 RCTs reported the number of participants with diarrhea, and the number randomized to both groups. Most trials did not show a statistically significant advantage for probiotic use. However, across the 63 RCTs (N = 11 811) probiotic use was associated with a lower relative risk (RR) of developing AAD compared with the control groups. (RR = 0.58; Number needed to treat = 13.)

Trials that reported incidence of AAD after cessation of antibiotic therapy reported that the number of patients experiencing AAD was lower in those who had received probiotics. (RR = 0.44)

No adverse effects were reported, and the probiotics were considered safe.

The main limitations of the study are unexplained heterogeneity, poor documentation of

probiotic strains, and lack of assessment of probiotic-specific adverse effects.

The study was not able to determine:

Any difference in response depending on age.

Which probiotic or combination resulted in greatest benefits.

The effect of probiotics treatment of AAD (ie, after start of symptoms).

Whether probiotic treatment is more effective in preventing *C difficile* AAD than other types of AAD.

If probiotics are entirely harmless.

Conclusion: Adjunct probiotic administration is associated with lower risk for AAD. This generalized conclusion likely obscures heterogeneity of effectiveness among the patients, the antibiotics, and the probiotic strains and blends.

JAMA MAY 9, 2012; 307: 1850-60 Original investigation, first author Susanne Hempel, RAND Health, Santa Monica, California

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*Obviously a weak study. How should the primary clinician respond?*

*What is the benefit / harm-cost ratio of probiotics? I believe it is high.*

*The harm is very low. Yoghurt has been used as a food for centuries. We should know any adverse events by now.*

*Costs are very low*

*Benefits may be great, especially if a case of *C difficile* colitis is prevented.*

*Should probiotics be used routinely when antibiotics are prescribed? I believe this should be a decision by the individual patient. If the patient enjoys yogurt and consumes it regularly, I see no reason not to suggest it. Certainly, it should be prescribed for patients who have experienced AAD before.*

*We still do not know much about probiotics to treat AAD once AAD has begun. It is worth a try.*

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## **BON DENSITY TESTING**

***Provides Evidence-Based Estimates For Osteoporosis Screening Intervals***

**1-2 BONE-DENSITY TESTING AND TRANSITION TO OSTEOPOROSIS IN OLDER WOMEN**

Current osteoporosis guidelines recommend routine bone mineral density (**BMD**) screening with dual X-ray absorptiometry (**DXA**) for women age 65 and older. None specify the interval of screening based on longitudinal cohort studies.

The goal is to detect low BMD before the onset of fragility fracture.

This study determined how the BMD testing interval related to the time of the transition from normal BMD, or osteopenia, to the development of osteoporosis, before hip or clinical vertebral fractures occurred.

Followed 4957 women age 67 and older (99% white) for up to 16 years. Subjects were recruited between 1986 and 1988. None had osteoporosis at baseline. None had a history of hip or clinical vertebral fracture. The follow-up period included examinations at years 2, 6, 10, and 16.

Defined the BMD testing interval as the estimated time during which osteoporosis developed in 10% of women before they had fractures, and before they received treatment for osteoporosis.

Stratified participants into groups according to the T-score at the femoral neck and hip:

- 1) Normal BMD (T-score  $\geq -1.00$  or higher)
- 2) Mild osteopenia (T score  $-1.01$  to  $-1.49$ ).
- 3) Moderate osteopenia (T-score  $-1.50$  to  $-1.99$ )
- 4) Advance osteopenia ( T-score  $-2.00$  to  $-2.49$ )
- 5) Osteoporosis (T-score  $\leq -2.50$  and lower)

Cumulative incidence of osteoporosis, over 16 years, according to baseline T-score:

	%
-1.00 or higher	10
-1.00 to -1.45	10
-1.50 to -1.99	49
-200 to -2.49	80 ( <i>My take on figure 2. Ed.</i> )

The adjusted estimated time for 10% of the women to transit to osteoporosis :

Normal BMD to osteoporosis	16 years
Mild osteopenia to osteoporosis	16 years.
Moderate osteopenia to osteoporosis	5 years
Advanced osteopenia to osteoporosis	<b>1 year</b>

The estimated time for 2% of women to have a hip or clinical vertebral fracture was more than 15 years for women with a normal BMD or mild osteoporosis, and 5 years for those with moderate or advanced osteopenia.

If BMD testing is deferred for 15 years among women with T-scores greater than -1.50, there is low likelihood of transition to osteoporosis during that period. For those with moderate osteopenia the transition time to osteoporosis for 10% of the women was 5 years, and 1 year for those with advanced osteopenia.

Recent controversy over the harms of excessive screening for other chronic diseases (breast cancer, prostate cancer, and cervical cancer) reinforce the importance of developing a rational screening program for osteoporosis. This study provides evidence-based estimates for the osteoporosis screening intervals before new hip or clinical vertebral fractures and before initiation of treatment for osteoporosis. Frequent BMD screening is unlikely to improve fracture prediction.

Conclusion: Osteoporosis would develop in less than 10% of older postmenopausal women during screening intervals that are set at: 15 years for those with normal BMD or mild osteopenia; 5 years for women with moderate osteopenia; and 1 year for those with advanced osteopenia.

NEJM January 9, 2012; 366: 225033 Original investigation, first author Margaret L Gourlay, University of North Carolina, Chapel Hill

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*The authors seem to suggest that treatment should begin at onset of osteoporosis. I believe many clinicians would begin treatment at an earlier stage—when moderate or advanced osteopenia is present.*

*Certainly many elders should receive prophylactic vitamin D and calcium.*

*The major contribution of this article is to guide frequency of screening. Screening is expensive and burdensome. It is often done too often without thought of benefit.*

*The recently published Physician Ethic Manual includes the ethical obligation to society to use health care resources carefully:*

*Physicians have a responsibility to practice effective and efficient health care, and to use health care resources responsibly. Parsimonious care that utilizes the most efficient means to effectively diagnose a condition and treat a patient respects the need to use resources wisely.*

[“Review of the American College of Physicians Ethical Manual” Annals Internal Medicine January 3, 2012; 156: 56-57]

## **CARDIOVASCULAR DISEASE**

### ***Primordial Prevention Vs Primary Prevention***

#### **1-1 LIFETIME RISKS OF CARDIOVASCULAR DISEASE**

In recent decades, efforts to reduce cardiovascular disease (CVD) have emphasized the importance of calculating global, short-term (generally 10-year) risk estimates. However, many adults who are considered at low risk for CVD in the short-term are actually at high risk across their remaining life span. Estimating lifetime risk provides a more comprehensive assessment of the overall burden of the disease in the general population. It takes into account both the risk of CVD and competing risks (eg death from cancer) until old age.

This study collected and pooled data from longitudinal epidemiological studies of cohorts conducted in the US over the past 50 years. And estimated the lifetime risk of CVD events according to age, sex, and other risk factors. It included 17 studies (n = 67 890 participants) in a pooled analysis. Determined deaths from CVD, from coronary heart disease, and from any cause. And non-fatal CVD events including myocardial infarction and stroke.

Risk factor levels were aggregated in accordance to 5 mutually exclusive groups:

- 1) All risk factors optimal—total cholesterol less than 180; untreated BP less than 120/80; no smoking; no diabetes.
- 2) At least one risk factor not optimal—total cholesterol 180-199; or untreated BP 120-139/80-89; no smoking; no diabetes.
- 3) At least one risk factor elevated—total cholesterol 200-239; or BP 140-159/90-99; no smoking; no diabetes.
- 4) One major risk factor present—current smoking; diabetes; total cholesterol at least 240; or BP 160/100 or more
- 5) Two or more major risk factors present.

At all ages, the prevalence of participants in the lowest risk group (all factors optimal) was small (under 5%). Only about 12% could be considered “normal”. (Optimal or only one factor not optimal) Over 2/3 had one or two major risk factors.

At age 55: (risk factor status)	1)	2)	3)	4)	5)
Death from CVD (%)	5	9	13	18	30
Total atherosclerotic CV events (%)	15	20	34	33	47

For participants age 45 and 55, lifetime risks are reported to age 80.

There were marked differences in the observed risks of death from CVD and total CVD events according to the risk burden. Outcomes were similar for other ages. (45; 65; 75)

In the cohort at index age 55, during 731 615 patient years of follow-up, there were 5912 deaths from CVD and 9391 non-fatal events related to CVD.

Those with optimum risk profiles had substantially lower risk of death from CVD through age 80 than those with 2 or more major risk factors (5% vs 30%). And lower lifetime risks of fatal coronary heart disease and non-fatal myocardial infarction (4% vs 38%).

Difference in risk of fatal and non-fatal stroke was less striking (2% vs 8%).

Lifetime risks tended to be very low among persons who had an optimal risk-factor profile at all index ages. Lifetime risks became substantially higher once any risk factor level was not considered optimal, with stepwise increases in remaining lifetime risk across groups with less favorable profiles for aggregate risk.

In general, the lifetime risk of death from CVD and CHD or non-fatal MI was about twice as high among men as among women.

These data strongly reinforce the influence of traditional risk factors on the lifetime risk of CVD. Even a relatively low burden of these risk factors was associated with significant increases in the long-term risk of CVD. Participants who have none of these risk factors had a very low lifetime risk.

These findings have important implications for clinical disease prevention and for public health. Efforts to lower the burden of CVD will require prevention of the development of risk factors (primordial prevention) rather than the sole reliance on the treatment of existing risk factors (primary prevention).

These data are consistent with suggestions that the decline in CVD events in the general population reflects changes in the prevalence of risk factors rather than the effect of treatment alone.

Conclusion: Differences in baseline risk-factor burden translate into marked differences in the lifetime risk of CVD. The differences are consistent across race and birth cohorts.

NEJM January 26, 2012; 366: 321029 Original investigation, first author Janet D Berry, University of Texas Southern Medical Center, Dallas

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*CVD is largely preventable. But, it remains the most common cause of death.*

*The low risk in those with optimal risk factor status is striking. Risk rises rapidly, by a factor of 3 to 6, as a few risk factors are added.*

*Treatment of risk factors results in major benefits. However, it may be better not to develop risk factors in the first place. How does one gain “primordial” prevention? It must be genetic plus years of healthy living.*

### ***Primordial Prevention Begins In Early Life***

#### **3-1 IMPROVING CARDIOVASCULAR HEALTH IN THE US POPULATION**

The American Heart Association has announced a new strategy to improve cardiovascular health by 20% by 2020 while reducing death from CVD by 20%.

Seven health behaviors and health factors define cardiovascular health: Not smoking; being physically active; having normal BP, blood glucose, total cholesterol, and weight; and eating a healthy diet.

Two key concepts are central to the development and achievement of the AHA goals:

1) At present, prevention efforts focus on unhealthy individuals and populations. But, most CVD events occur in the large proportion with average or only mildly elevated levels of risk factors, rather than the small subset with marked elevations. Thus, in addition to the “high risk” strategies, population strategies must shift the entire population distribution of risk factors toward more favorable levels. When population strategies are successful, small changes in population levels can result in large reductions in disease rates.

2) Population strategies that prevent risk factor development in the first place are called *primordial prevention*. Once a risk factor has developed, it is difficult to reduce risk back to a low level. Pharmacological and lifestyle interventions for primary and secondary prevention, while effective, will not reduce cardiovascular (CV) event rates to levels seen in patients who maintain optimal risk profiles from youth into middle and older age.

An article in this issue of JAMA<sup>1</sup> reported secular trends in CVD health metrics in the US over the past 20 years. The prevalence of all 7 factors at ideal levels was less than 2%. There were some positive trends; Increases in physical activity; reductions in smoking, BP, and cholesterol levels. There were alarming trends: Decreased proportion of adults following a healthy diet; and increased prevalence of obesity and impaired fasting glucose.

The data indicate the critical importance of attempting to shift the population toward greater CV health. There was an association between the numbers of ideal health metrics and mortality over 15 years. Compared with individuals with 0 or 1 metrics at ideal levels, those with 6 or 7 had over 50% lower all-cause mortality, lower risk of premature CVD death, and even a reduction in some cancers.

Why do so few Americans have ideal CV health? The answer is clear.

Data from all of the studies indicate that the face of ideal CV health is young, educated, white women. The pattern of ideal CV health is normal in most infants, but it is lost, sometimes rapidly, during childhood, adolescence, and young adulthood through adoption of adverse behaviors related to diet, weight, and sedentary lifestyle, particularly in populations with lower socio-economic status. Thus the nature of the problem transcends the public health care system. Solutions must come from improvements in the environment and better access to healthy food and activity, which should reduce the alarming disparities in cardiovascular health.

A concerted effort is needed to improve health behaviors in all segments of the population. Opportunities abound for physicians, policymakers, and consumers to support improvements in CV health.

JAMA March 28, 2012; 307: 1314-16 Commentary by Donald M Lloyd-Jones, Northwestern University Feinberg School of Medicine. Chicago, IL

1 “Trends in Cardiovascular Health Metrics and Associations with All-cause Mortality Among US Adults” JAMA March 28, 2012; 307: 1273-83 Original investigation, first author Quarnhe Yang, CDC. Atlanta, GA.

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*Most interventions have been focused on primary and secondary prevention. The term “primordial prevention” is new to me. Primordial prevention is the real goal.*

*This is a challenge for primary care. We relate to the general population to a greater extent than any other specialty. But each of us relates to one patient and family at a time. We can make a difference by educating individuals and families, especially those with young children.*

*Our efforts, however, will be meaningless unless we act as role models and adopt all 7 metrics ourselves.*

*I believe there is a role for government in improving the food supply to lower adverse fats, salt, and sugar. There is also a great challenge for our school systems to teach primordial prevention.*

*I have abstracted several articles recently promoting preventive care, especially lifestyle interventions. I make no apology for the repetition. The subject is so important.*

***Medicine Must Negotiate A Precarious Bargain. Primary Prevention Of Disease Is A Philosophical Question, Just As It Is A Medical Question.***

**4-5 CARDIOVASCULAR PRIMARY PREVENTION**

These editorialists argue that the bar for treatments for primary prevention must be raised. Long-established preventive practices (based on biomarkers and surrogate endpoints) may be erroneous. Large randomized, controlled trials must show that the primary prevention treatments improve mortality and morbidity before implementation.

Surrogate endpoints disagree with hard (clinical) outcomes, and with each other.

These contradictions further undermine our ability to trust surrogate endpoints (improvement in biomarkers). They force us to confront a very difficult question—should we demand that cardiovascular agents improve morbidity and mortality before being used in primary prevention?

Primary prevention is unlike so much of medicine because it is performed in asymptomatic patients in their efforts to live longer and better and to delay onset of symptoms. When primary prevention is prescribed, a question remains—is it introduced in error? Empirical evidence suggests that nearly half of trials testing standards of care ultimately do not support the practice and constitute medical reversals.

Medicine must negotiate a precarious bargain—accepting promising, but unproven, therapies for primary prevention, sorting them out in the decades that follow, or, alternatively, setting a high barrier for primary prevention and implementing only preventions that have met the requirement to reduce morbidity and mortality.

Primary prevention makes sense when a disease is prevalent, when there is an effective therapy, and when there is evidence that early action leads to improved clinical outcomes beyond what might be achieved with later treatment. What counts as effective therapy? There should be evidence from randomized, controlled trials showing that the screening program and preventive treatment improves morbidity and mortality.

Archives Internal Medicine April 23, 2012; 172: 656-59 “Special Article” first author Vinay Prasad. Northwestern University, Chicago, Ill

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*Much of primary care medicine is based on identifying and treating risk factors (biomarkers; surrogates for clinical events). Then, if they are elevated, applying some preventive treatment. If we treat the biomarker and reduced risk, we assume we have benefited the patient.*

*For example, if the patient's BP (a biomarker; a risk factor) is high, we treat to lower it into "normal" range. But there is no way we can determine if the preventive treatment actually prevents a stroke in an individual patient. The best we can do is to inform him that the chances are that treatment will, over the observation time, reduce the incidence of stroke by 1 in XXX, based on the number needed to treat (NNT) demonstrated in long-term randomized trials. If the patient develops a stroke, he bore the expense and harms of the drug without benefit.*

*Off hand I can think of at least 10 commonly applied risk factors (biomarkers). Often a patient will have several risk markers. Treatment with drugs inevitably places the patient at harm from long-term adverse drug effects and costs.*

*Millions and millions of patients in the US are taking preventive drugs at a cost of billions and billions. (Do not underestimate the power of marketing departments of drug companies.) But, we cannot determine benefits in an individual patient.*

*Nevertheless, we continue to rely on treatment of biomarkers. I believe they have brought benefits to patients. As the editorialists suggest, we cannot reasonably wait for proof of clinical benefits for drugs. We are stuck with treatment of biomarkers.*

*Not all patients considered for primary prevention and treatment are equal. Some can be classified at low risk; some at high risk. We should concentrate on the latter. Primary care clinicians must make a judgment call. How aggressive should we be?*

*Secondary prevention is more straightforward.*

*Lifestyle interventions are associated with the highest benefit / harm-cost ratio, far exceeding drug therapy. I keep coming back to a healthy lifestyle as the basic preventive therapy.*

## **CHOLESTEROL**

***Non-HDL-C Had A Stronger Association With Risk Of Major CV Events Than LDL-C And Apo-B***

### **3-4 ASSOCIATION OF LDL-CHOLESTEROL, NON-HDL CHOLESTEROL, AND APOLIPOPROTEIN- B LEVELS WITH RISK OF CARDIOVASCULAR EVENTS AMONG PATIENTS TREATED WITH STATINS: A Meta-analysis**

All current guidelines state that low-density lipoprotein cholesterol (**LDL-c**) levels should be used as the target to initiate and titrate lipid-lowering therapy.

LDL- c may not be the best lipid parameter to predict CV risk or to quantify the atheroprotective effect of statin therapy.

This study was based on 8 randomized controlled trials including 38 153 participants. All

participants included were taking statin drugs.

*(This was a high risk group of patients who were receiving primary or secondary preventive therapy. Many had experienced a CV event. Ed.)*

Measured total-c, LDL-c, Apo-B, HDL-c, and triglycerides at baseline and at 1 year. Non-HDL-c was calculated as total-c minus HDL-c.

Followed for major CV events: Myocardial infarction (fatal and non-fatal), coronary artery disease, unstable angina, stroke (fatal and non-fatal), peripheral arterial disease, and congestive heart failure.

Calculated hazard ratios (**HR**) for risk of major CV events by 1 standard deviation (**SD**) from the mean of LDL-c, Apo-B, and non-HDL-c. Determined one SD for non-HDL-c to be 36 mg/dL; LDL-c to be 32 mg, and Apo-B to be 27 mg.

During follow-up, among the 38 153 participants 14% experienced a CV event.

LDL-c, non-HDL-c and Apo-B were statistically associated with risk of major CV events:

	One standard deviation: mg/ dL	HR for each 1 SD increase
LDL-c	32	1.13
Non-HDL-c	36	1.16
Apo-B	27	1.14

HRs for risk of major CV events for 4 patient categories comparing non-HDL-c with LDL-c defined by target levels of 130 mg/dL and 100 mg/dL.

LDL-c	Target	HDL-c	HP
> 100 mg/dL	> 100	> 130	1.21
<100	> 100	>130	1.32
>100	<100	<130	1.02
<100	<100	<130	1.00 (Referent)

Compared with those who reached both targets, statin treated patients reaching the non-HDL-c target of < 130, but not the LDL-c target of <100, had a HR of major CV disease of 1.02. Patients reaching the LDL-c target, but not the non-HDL-c target had a HR of 1.32.

*(Ie, reaching the non-HDL-c target seems much more protective. ED.)*

“Our observation in statin-treated patients extended prior results from large population-based

studies showing that non-HDL-c is more strongly associated with risk of future major cardiovascular events than LDL-c.” The study did not find evidence that Apo-B performed better than LDL-c or non-HDL-c.

Conclusion: Among high-risk, statin-treated patients, on-treatment levels of LDL-c, Apo-B and non-HDL-c were each associated with risk of future major CV events. The strength of the association was greater for non-HDL-c than for LDL-c and Apo-B.

JAMA March 28, 2012; 305:1302-09 Original investigation, first author S Matthijs Boekholdt Academic Medical Center, Amsterdam, Netherlands

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*A provocative study, but not conclusive. Determination of the best and least expensive marker for effectiveness of statin therapy is an important challenge for primary care. To abide by the ethical principle of good stewardship of medical interventions and costs, we must choose the simplest and most cost effective marker. Certainly it will not be the combined LDL-c + non-HDL-c. I would bet on non-HDL-c.*

## **CHOOSING WISELY**

***Clearly, There Are Areas In Which Health Care Spending Does Not Add To The Health Of Individuals Or Communities.***

### ***5-5 CHOOSING WISELY: Helping Physicians And Patients Make Smart Decisions About Their Care***

The US is grappling with the costs of health care and quality care. Clearly there are areas in which health care spending does not add to the health of individuals or communities.

An initial focus should be on the overuse of medical resources, which is not only a leading factor on the high level of spending on health care, but also places patients at risk of harm. Some estimates suggest that as much as 30% of all healthcare spending is wasted.

Physician’s decisions about tests and procedures account for about 80% of health care expenditures. Yet physicians do not always have the most current effectiveness data. They can recommend diagnostic and therapeutic interventions that are no longer considered essential. Physicians may need help in communicating these matters to their patients. This may be especially difficult when clinicians and consumers are deluged with advertising and promotions. Physicians often

report feeling compelled to accommodate patient's requests for interventions they know are unnecessary.

Patients need trustworthy information to help them better understand that more care is not always better care, and in some cases actually cause more harm than good. Patients need transparent and creditable information about the relative value and risks of various diagnostic and therapeutic interventions

To help reduce waste in the US health care system, and promote physician-patient conversations about making wise choices, 9 medical specialties have joined the *American Board of Internal Medicine Foundation* and *Consumer Reports* in the first phase of the "choosing wisely" campaign. Each society developed a list of 5 treatments or tests that are commonly used, which should be re-evaluated. The lists were released in April 2012 at a national event in Washington. It articulated the professional responsibility of physicians to improve quality and access to care, and to advocate for just and cost-effective distributing of finite resources. It specifically calls on physicians to be responsible for the appropriate allocation of resources and to avoid superfluous tests and procedures.

In 2010, a *Consumer Report* survey of nearly 12 000 healthy 40- to 60-years old men and women with no heart disease risk factors or symptoms, showed that 44% had received screening tests for heart disease that were unlikely to have benefits that outweigh harms. Those who received testing did so without first getting crucial information from their physician. Only a few patients discussed with their physician how accurate the tests were, whether they reduced mortality, the potential complications that might occur due to the tests, or what the patient would need to do if the tests indicated a problem.

There is need to dispel the myth that "if some medical care is good, more is better".

The hope is that the lists will spark discussions between physician and patients about the need—or lack thereof—for many frequently ordered tests and treatments.

*Consumer Reports*, an independent non-profit consumer organization, in consultation with professional societies, will create and disseminate consumer-friendly versions of the lists to help patients understand the recommendations and be prepared to talk with their physicians about them.

The medical organizations demonstrate leadership, vision, and courage in highlighting overuse in their specialty. This is the highest form of medical professionalism.

The complete lists can be found at <http://www.choosingwisely.org>

Also see Consumer Reports – acting wisely

JAMA May 2, 2012; 307: 1801-02 First author Christine K Cassel, ABIM Foundation, Philadelphia, PA

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*This is a good start—a work in progress. The goal is to achieve just and cost-effective distribution of finite clinical resources. We must be good stewards of medical interventions and costs. This is an ethical imperative.*

*It may take decades of experience with tests to determine the benefit / harm-cost ratio. Note the long debate about the value of prostate-specific antigen testing. And screening mammography in women age 40-49.*

## **COFFEE DRINKING**

***A Dose-Dependent Inverse Association Providing Assurance That Coffee Does Not Adversely Affect Health.***

### **4-4 ASSOCIATION OF COFFEE DRINKING AND TOTAL AND CAUSE-SPECIFIC MORTALITY**

Results of previous studies relating coffee drinking (CD) to total mortality have been inconsistent. This is possibly due to inconsistent control for possible confounders and the small number of deaths.

This study used data from a very large cohort to determine whether CD is associated with total and cause-specific mortality. The study had ample power to detect even modest associations and allowed for subgroup analysis according to important baseline factors.

Between 1995-1996, over 617 000 persons returned a comprehensive questionnaire assessing diet and lifestyle. After exclusions, the study included 229 119 men and 173 141 women--age range 50-71 (median age 62) at baseline. None had cancer or cardiovascular disease.

The baseline questionnaire assessed demographic and lifestyle characteristics, including 124 dietary items. Coffee consumption was assessed only one time (at baseline).

Multivariate models were adjusted for multiple baseline factors, including smoking, BMI, age, alcohol consumption, consumption of fruit and vegetables, red meat, saturated fat, and other possible confounders.

During 14 years of follow-up (over 5 100 000 person-years) 33 731 men and 18 784 women died. After multivariate adjustments for potential confounders, a modest inverse association between CD and total mortality was observed for both men and women.

Hazard ratios (HR) for all-cause mortality among those who drank coffee, compared with those who did not drink coffee:

	None	< 1 cup/d	1 cup	2-3 cups	4-5 cups	6 or more
Men	1.00	0.99	0.94	0.90	0.88	0.90
Women	1.00	1.01	0.95	0.83	0.84	0.85

CD and cause-specific mortality: After multivariate adjustment, CD appeared to be inversely associated with most major causes of death in both men and women, including heart disease, respiratory disease, stroke, injuries and accidents, diabetes, and infections.

Smoking negates whatever benefit CD may have.

Associations between CD and death from cancer were not significant for any single category of coffee consumption.

In this large prospective cohort, there was a dose-dependent inverse association between CD and total mortality after adjusting for potential confounders.

As compared with men who did not drink coffee, men who drank 6 or more cups of coffee daily had a 10% lower risk of death. Women had a 15% lower risk.

There was no difference in outcomes between caffeinated and decaffeinated coffee.

Given the observational nature of this study, it is not possible to conclude that the inverse relationship reflects cause and effect.

Conclusion: There was a significant inverse association of CD with death from all-causes and specifically with deaths due to heart disease, stroke, respiratory disease, injuries and accidents, diabetes and infections. These results provide assurance that CD does not adversely affect health.

NEJM May 17, 2012; 366: 1891-1904 Original investigation, first author Neal D Freedman, National Institutes of Health Rockville MD The National institutes of Health-AARP Dietary Health Study

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*This is a massive study. I congratulate the investigators on their deduction.*

*The difficulty observational studies have is in controlling for multiple possible confounding factors. The investigators did their best, but some doubt remains.*

*Concerning accidents and injuries, I believe caffeine may have some influence. It increases awareness and decreases drowsiness. This increases safety on the highway and in the home and shop.*

*The investigators mentioned the manner of preparation of coffee. Boiled coffee promoted dyslipidemia. Filtered coffee does not.*

*It is refreshing to learn that a pleasurable lifestyle intervention actually promotes health.*

## **COLORECTAL CANCER**

***Supports The Hypothesis That Colonoscopic Removal Of Adenomas Prevents Death From CRC.***

### **2-1 COLONOSCOPY, POLYPECTOMY AND LONG-TERM PREVENTION OF COLORECTAL CANCER**

Screening for colorectal cancer (CRC) affects mortality in 2 ways: 1) Detecting cancer at an early, curable stage, and 2) More commonly, detecting and removing precancerous adenomas.

This study is a continuation of the National Polyp Study (NPS; 1980-1990), which examined whether polypectomy would reduce the incidence of death from CRC. It is a long-term follow-up study (up to 23 years) to determine the mortality from CRC in the general population vs the observed rate of CRC deaths among patients with adenomatous polyps that had been removed.

The NPS was a multicenter post-polypectomy surveillance study of patients who had one or more newly diagnosed adenomas removed. It involved 7 clinical centers that represented a wide range of endoscopic practices.

The long term follow-up analysis entered 2602 individuals in whom adenomas had been removed. Individuals were followed to determine the incidence of death from CRC.

Used the National Death Index to identify deaths and to determine the death rate and the cause of death in the general population.

Mortality from CRC among patients who had adenomas removed was compared with the expected mortality from CRC in the general population with similar age, sex, race and calendar year.

The end point was a comparison of death from CRC in both groups,

Baseline characteristics of 2602 individuals who had adenomas removed: Mean age 62; 66% male; advanced adenoma 57% (diameter over 10 mm; tubulovillous or villous; high grade dysplasia).

The median follow-up was 16 years with a maximum of 23 years.

There were 12 deaths from CRC in the adenoma cohort. And 25 estimated deaths in the general population over 20 years. Mortality rose after the first 4 years.

The cumulative 20-year mortality in the adenoma cohort was 0.8% vs an estimated 1.5% in the general population.

Conclusion: The findings support the hypothesis that colonoscopic removal of adenomas prevents death from CRC.

JAM February 23, 2012 | 366: 687-96 Original investigation, first author Ann G Zauber, Memorial Sloan-Kettering Cancer Center, New York.

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*This is not a strong study. No direct comparison was made between the 2 groups. Nevertheless, I believe most clinicians would accept the conclusion of the study, knowing the long observed adenoma-carcinoma sequence.*

*By my rough calculation from their data, about 200 patients would undergo polypectomy to prevent one death from CRC.*

*The study also considered a group of patients who had non-adenomatous polyps removed. I omitted these data.*

### ***Both Have Advantages And Disadvantages***

## **2-2 COLONOSCOPY VERSUS FECAL IMMUNOCHEMICAL TESTING IN COLORECTAL CANCER SCREENING**

Several studies have shown that CRC screening is effective and cost-effective in the average risk population. There are two recommended strategies for screening: 1) Stool testing—occult blood [eg, fecal immunochemical testing **FIT**] and 2) Structural examination (flexible sigmoidoscopy, computed tomography, and colonoscopy).

Recent evidence suggests that, in patients in whom one normal colonoscopy is reported, risk of CRC is markedly reduced.

Comparative studies have shown that semi-quantitative FIT is more accurate than guaiac in detecting CRC and advanced adenomas. This test is now recommended as a first-choice stool screening examination.

Although FIT is less effective for detection of neoplasms than colonoscopy, it may be better accepted by the public. Higher acceptance may counteract its lower detection capacity. FIT may be more effective and less costly than other screening strategies.

This randomized, controlled trial compared FIT with colonoscopy. The investigators hypothesized that FIT screening every 2 years would be non-inferior to one-time colonoscopy in reducing mortality from CRC among average risk patients.

This is a preliminary report of a proposed 10-year trial.

Randomized to: 1) one-time colonoscopy or 2) FIT stool examination to be done every 2 years. The study was based on the hypothesis that screening average-risk subjects with biennial FIT would not be inferior to one-time colonoscopy in respect to the rate of death from CRC at 10 years.

Those with a positive FIT were referred for colonoscopy.

Over 57 000 subjects underwent randomization. (Average age 59; 53% women.) Only about 18% of those randomized to colonoscopy underwent colonoscopy; 37% of those assigned to FIT received FIT.

Among subjects screened by FIT, 7% tested positive. All were referred for colonoscopy; 86% actually underwent colonoscopy.

As screened analysis after exclusions and refusals, and some cross-overs:

	Colonoscopy	FIT
Number	5059	10 507
Cancer (%)	27 (0.5)	36 (0.3)
Advanced adenoma	493 (9.7)	252 (2.4)
Non-advanced adenoma	1116 (22)	112 (1.1)
Any neoplasm	1636 (32)	400 (4)

The most relevant result of this interim analysis was that one-time screening with FIT was very similar to one-time colonoscopy with respect to rate of detection of CRC. (0.5% vs 0.3%) There was no significant difference in the stage of cancers detected.

Conclusion: In this interim analysis, patients randomized to the FIT group were more likely to participate in screening. The number of CRCs detected was similar in the 2 groups. More adenoma were detected in the colonoscopic group.

NEJM February 23, 2012; 366: 692-706 Original investigation by the COLONPREV Study, first author, Enrique Quintero, Hospital Universitari, Tenerife, Spain.

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*The article reports the intention-to-treat results at length. I omit these because I believe primary care clinicians are much more interested in results based on subjects who actually receive the test.*

*The FIT stool screening test is based on specific antibodies to globulin. It is more effective in outcomes and costs than guaiac testing. It reports quantitative results, detecting down to 0.3 mL of blood. It does not detect bleeding from the upper GI tract and thus is more specific to colo-rectal bleeding. Source: Wikipedia*

*The FIT test in this study was done on the automated semi-quantitative OC-Sensor machine (Eiken Chemical)*

*The trial analyzed stool samples with the use of an automated semi-quantitative OC-Sensor (Eiken Chemical) without specific dietary restriction or medication use.*

*Stool testing for exfoliated DNA is being developed. I believe further experience is required.*

*The investigators argue that biannual FIT exams are made more acceptable than colonoscopy simply because many more patients will accept FIT. (Better a less sensitive test than no test at all.) If repeated every 2 years, more adenomas and CRCs will be detected.*

*The authors stated that about 1 in 3 subjects had a neoplasm (cancer, advanced adenoma, non-advanced adenoma). This seems high to me.*

*They also state that detection of CRC (0.5 by colonoscopy vs 0.3 by FIT were clinically similar, I disagree. This amounts for 2 cancers per 1000 which remained undetected by FIT.*

*Perhaps a one-time normal colonoscopy followed by biennial FIT exam will turn out to be an acceptable, cost-saving approach.*

*The most effective and cost-effective screening strategy for CRC is to be determined.*

### ***Incidence Of CRC Was Reduced By 21% And Mortality By 26%***

## **6-2 COLO-RECTAL CANCER INCIDENCE AND MORTALITY WITH FLEXIBLE SIGMOIDOSCOPY**

This trial studied the effect of screening flexible sigmoidoscopy (FS) on the incidence of distal and proximal colo-rectal cancers (CRC) and related mortality.

Enrolled 154 900 men and women age 55 to 74 from 1993 through 2001. None had previous cancers. Most participants were offered FS every 5 years. An examination was considered positive if a polyp or mass was found. Biopsies were not routinely performed. Participants with a polyp or mass were referred to their primary care physician for decisions about diagnostic follow-up, a diagnosis of cancer, and cancer complications.

Death from CRC was the primary endpoint. Mean follow-up = 11 years

CRC incidence and CRC mortality according to study group.

	FS (N = 77 445)		Usual care (N = 77 455)		RR <sup>a</sup>
	No.	Rate per 10 000 Person-years	No.	Rate per 10 000 Person-years	
Incidence					
Total CRC	1012	11.9	1287	15.2	0.79

## Mortality

Total CRC	252	2.9	341	3.9	0.74
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(a Relative Risk [RR])

In absolute terms: (*My estimates from their data. Ed..*)

Mortality from CRC decreased by about 1 per 1000 persons screened by FS.

Incidence of CRC decreased by 3 per 1000 screened by FS .

The number needed to invite for screening in order to prevent one CRC death was 871.

Among patients with screening-detected CRC, 83% were distal. Among those who were never screened, 53% of CRCs were distal.

Participants with screen-detected CRC were more likely to have earlier stage cancers (stage I or II) than participants who were never screened.

Mortality related to distal CRC was reduced by 50% and the incidence was reduced by 29%.

The investigators estimated that colonoscopy screening (vs. FS) would have increased the number of screen detected CRCs by about 16%.

Conclusion: Screening with FS, in conjunction with colonoscopy was associated with clinically important decreases in CRC incidence and mortality. A significant reduction in mortality was observed only for CRC in the distal colon. The incidence of CRC was reduced in both the distal and proximal colon

NEJM June 27, 2012; 366: 2035-57 Original investigation by The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening trial, first author Robert E Schoen, University of Pittsburg Medical Center, Pittsburg, PA

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*Any screening that reduces mortality by 1 in 1000 over 10 years is noteworthy.*

*The trial was “contaminated”. Ie, there were many protocol violations. Many participants in the usual care group crossed-over and received FS and colonoscopies. Many of those randomized to the intervention group did not undergo FS. Only about half received a second FS. Some with positive FS findings did not go on to receive colonoscopy.*

*I believe more strict compliance with a screening protocol would result in more lives saved.*

*What should the frequency of FS be? “Choosing wisely” in an effort to reduce medical costs and improve patient care, suggested every 10 years after a completely normal colonoscopy in average risk patients. And every 5 years after complete removal of one or two small adenomas without high grade*

*dysplasia. The same should apply to FS. However, if these adenomas were discovered by FS, the protocol of this trial calls for colonoscopy.*

*The greatest advantage of screening FS vs screening colonoscopy is population acceptance, lower costs and wider availability. Many more patients would be willing to undergo a FS and would refuse colonoscopy.*

*Preparation for FS is less intrusive, usually enemas and dulcolax. Sometimes magnesium citrate. No sedation was used. (Personal communication Dr. Robert Schoen.)*

## **DIABETES**

### **6-3 PREDIABETES: A High-Risk State For Diabetes Development**

Prediabetes (**PD**; pre-type-2 diabetes) is a high risk state for diabetes mellitus type-2 (**DM-2**). PD is defined as higher than “normal” fasting plasma glucose, but lower than the threshold for diabetes.

Diagnostic criteria for PD have changed over time and vary depending on the institute of origin. The ADA defined PD:

- 1) Fasting plasma glucose (FPG) of 100-125 mg/dL. (126 and higher is DM-2.)
- 2) Or an impaired glucose tolerance: Plasma glucose, 2-hours after 75 g oral glucose, between 140- 200 mg/dL. (Over 200 = DM-2)
- 3) Or Hemoglobin A1c of 5.7% -6.4%

The NHANES suggested that 35% of US adults older than 20 years and 50% of those over 65 had PD in 2008.

According to the ADA, up to 70% of individuals with PD will eventually develop DM--2.

Risk predictors include: age, BMI, waist circumference, high systolic pressure, hypertension, family history, smoking, physical inactivity, blood levels of glucose at the high end of the PD range, and triglycerides, uric acid, lipid levels.

A proposed model of progress from normo-glycemia to diabetes:

- 1) A long period of insulin resistance accompanied by a compensatory increased rate of insulin secretion and increased beta-cell mass.
- 2) A stable adaptation period when beta-cells are no longer fully compensating for increased insulin resistance. Fasting and post-load glucose are not completely maintained. This period probably starts when fasting and post-load glucose levels are still in the normal

range, and is usually accompanied by a decrease in acute insulin secretion at FBG concentrations of about 100 mg/dL.

(The first and second stages occur before the PD phase.)

3) During the unstable early PD period beta-cells become unable to compensate for insulin resistance. Blood glucose levels rise above normal.

#### 4. Manifest DM-2

A. Stable decompensation

B. Severe decompensation

In DM-2 patients, body glucose disposal is decreased, mainly related to muscle insulin resistance. If insulin secretion was able to compensate for insulin resistance, no change in glucose concentrations would occur. This means that, by definition, beta-cell dysfunction is already present in PD, and insulin secretion is decreased.

Numerous observational studies have reported evidence of associations between PD and neuropathy, nephropathy, retinopathy, and macrovascular events.

Lifestyle interventions: PD should be treated to prevent progression to DM-2. Lifestyle changes should be the cornerstone of treatment. Obesity and physical inactivity are the most important modifiable risk factors. Two large studies reported a 58% risk reduction after interventions aimed at weight reduction, dietary changes, and increased physical activity.

Drug therapy: Metformin is safe. No serious adverse effects (only mild GI effects) have been detected in the years of use. Its beneficial effect is greater in PD patients with higher baseline BMI and higher FBG.

Several trials support a long-term reduction in risk of DM-2 and a delay in onset of DM-2 as a result of lifestyle and drug interventions.

In view of its long-term safety, metformin could be given to people who cannot comply with lifestyle advice.

Lancet June 16, 2012; 379: 2279-90 Review article, first author Adam G Tabak. University College, London

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*I spent more time and effort abstracting this article than usual because of its importance as an application and opportunity for primary care.*

*DM-2 is preventable.*

*We need a better definitions for diabetes. It is now defined by blood levels, which are arbitrary and imprecise. Definitions differ and change over time. Diabetes type-2 is a state of insulin resistance leading to beta-cell stress and failure, increasing blood glucose levels, and organ damage. By this definition, some patients with PD actually have diabetes.*

*PD also requires a new definition. It is a very heterogeneous group. Differences in definition are still present after years of study.*

*Since DM-2 is defined by blood glucose levels, FBG must be determined by screening. Who should be screened? Certainly the high-risk groups of obese and sedentary patients. But, determination is so inexpensive and available, I believe most patients will be screened from time to time.*

*I believe metformin will delay incidence of DM-2 and may help to prevent it. Except for expense, trouble, and duration of therapy, I see no reason why it should not be prescribed in conjunction with lifestyle changes.*

*In the group of patients with PD, who are subject to develop DM-2, other risk factors for cardiovascular disease are likely present, and should be treated.*

*The challenge for prevention extends to physicians, some of whom are overweight and sedentary. We must be good role-models.*

### ***“Moving Away From Rigid Guidelines”***

## **6-4 GUIDELINES EASE UP ON GLYCEMIC CONTROL IN SOME PATIENTS WITH DIABETES**

Physicians are being told to loosen up on glycemic control when treating certain patients with type-2 diabetes mellitus (DM-2)

Aggressive glucose management has been a mainstay of treatment, intended to reduce microvascular risks. The traditional goal is keeping the HbA1c below 7.0%. But recent trials have suggested that achieving these goal puts certain patients at risk for cardiovascular complications and death.

The ADA released a report in April 2012 calling for a more patient-centered treatment approach that takes into account patient needs, preferences, and tolerances. The report noted that lowering HbA1c below 7.0% is still recommended in most patients. Less stringent goals, between 7.0% to 8.0%, are appropriate for patients with a history of severe hypoglycemia, limited life-expectancy, advanced complications, extensive co-morbid conditions, and those that have difficulty attaining the

7.0% goal despite intensive self-management, education, repeated consultations, and effective doses of glucose-lowering agents, including insulin.

The report adds that the goal of 6.5% might be considered in select patients with short DM-2 duration, long life expectancy and no significant cardiovascular disease, if the goal can be achieved without significant hypoglycemia.

These multiple targets emerged from a 2010 study that found a U-shaped risk curve. Those with the lowest rates of all-cause mortality had a HbA1c of 7.5%. Those with higher and lower levels had increased risk for all-cause mortality and cardiovascular events.

The ACCORD trial (2008) found that patients randomized to intensive therapy of 6.0% or lower were 22% more likely to experience a non-fatal myocardial infarction, non-fatal stroke, or death from CVD than those randomized to standard therapy with a target of 7.0% to 7.9%.

The goal of 7.0% came from a study of type-1 diabetes that found a target of 7.0% seemed to balance benefits and risks of glycemic control. But no study says that the target should be 7.0% for everyone.

The report also notes that lifestyle interventions (weight management, diet, and exercise) are key factors for minimizing complications of diabetes.

Another important element of the report addresses the growing array of pharmacological agents available for treatment of diabetes and their possible adverse effects. Metformin remains the optimal first-line drug. The report cannot say with certainty which additional drugs are better because of a “distinct paucity of long-term comparative effectiveness trials”.

The report should serve as one of the tools available to physicians and patients as they discuss treatment options. Moving away from rigid guidelines is probably best for individual patients. One of the problems of evidence-based medicine is that it can make physicians develop a one-size-fits-all approach. Less rigid guidelines allow flexibility to change treatment courses over a patient’s lifetime. People are different and their perspectives change. A continuing dialogue is important. Determine goals and tailor therapy, but adjust over time.

JAMA June 6, 2012; 307: 2243-44 Medical News and Perspective by Mike Mitka, JAMA staff.

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*Another example of treating the patient with the disease, rather than the disease alone.  
This applies especially to chronic co-morbid illnesses.*

*A benefit / harm-cost ratio applies to interventions in each individual patient at a given time. The ratio may change over time. Costs increase with age, not only in monetary terms, but also in inconvenience, bother, difficulty in understanding and following a treatment protocol, problems with transportation. The elderly have less to gain by a strict treatment protocol.*

*They have less time to benefit.*

*Individualism is a key point. Reaching goals must be tempered by good judgment.*

## **DYSLIPIDEMIA**

***We Do Not Know if The Long-Term Risk-Benefit Profile is Favorable Or Harmful***

### **1-4 UNIVERSAL SCREENING AND DRUG TREATMENT OF DYSLIPIDEMIA IN CHILDREN AND ADOLESCENTS**

Over the past few decades, the theory that adult disease begins in childhood has been widely discussed. Smoking, the most common cause of death in adults, usually begins before age 18. Obesity has become the largest health problem in the U.S. Childhood and adolescent obesity often carries over into adulthood.

There is good evidence that screening and treatment for hypertension and tobacco use during childhood and adolescence prevents later cardiovascular disease.

Development and progression of atherosclerosis often starts in childhood. But the recommendation for universal screening for lipid levels at ages 9-11, and again at 17-21 is controversial.

New guidelines issued in 2011 by an expert panel of the NHLBI (endorsed by the American Academy of Pediatrics) recommend both behavioral and drug therapy for dyslipidemia in children. There is robust evidence that high levels of LDL-cholesterol are a cause of atherosclerosis. But, this evidence is not matched by similar evidence that long-term (perhaps lifelong) drug treatment in children is effective and safe. The new guidelines are likely to result in an epidemic of cholesterol screening and lipid-lowering drug therapy in children.

Statin drugs are associated with large declines in coronary events and total mortality in adults. This has led to use of statins by millions of patients in the U.S. Their use in children is simply part of this historical trend. The expanded use of statins in new populations increases the opportunity of harm as well as benefit.

Statin drugs are not harmless. High dose simvastatin is associated with high rates of serious myopathy and rhabdomyolysis.

In evaluation of drug treatment for dyslipidemia, lipid levels have frequently been used as surrogate end points. However, the use of surrogate endpoints to infer actual health benefits is one of the most serious potential biases in the design of studies used in the drug-approval process. Any putative benefits of statins in children are based on surrogate, not clinical, endpoints. Drug-induced lipid-lowering effects are not necessarily tightly linked to actual health benefits.

In children, clinical trial evidence of statin use is limited to small groups of subjects with limited duration. And only surrogate outcomes (eg, LDL-cholesterol) have been observed. Clinical health benefits and unexpected adverse effects in children have not been established. The absence of compelling evidence of a favorable risk-benefit profile for drug treatment makes the clinical decision difficult.

The expert panel recommends a complex algorithm for treatment of dyslipidemia in children. The new recommendation for universal screening may divert attention away from other important parts of the report, including diet and physical activity.

What this novel public health intervention in children clearly lacks is an evaluation to determine whether the long-term risk-benefit profile may in fact be favorable or harmful.

JAMA January 18, 2012; 257-58 “Viewpoint”, editorial, first author Bruce M Psaty University of Washington, Seattle.

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*We simply do not know the benefit / harm-cost ratio of screening and treatment for dyslipidemia in children and adolescents. Studies of children have been limited to small groups and of short duration. We know something about benefits, and more about costs, but little about harms of life-long drug treatments.*

*Harms of drugs may takes years to become evident. These are usually less common adverse effects. But, if millions of patients take the drug, even if adverse effects are rare, many patients will be harmed. Recently statins have been reported to be associated with increased risk of cognitive problems and diabetes.*

*(“Statin Use And Risk Of Diabetes Mellitus In Postmenopausal Women In The Women’s Health Initiative” Archives Internal Medicine January22, 2012)*

*I believe it does little good to lower LDL-c to “target” (target unspecified) in young persons unless smoking, body mass index, and diet are controlled. And development of type-2 diabetes is*

*prevented as long as possible. Certainly lifestyle interventions are more applicable in children than drug treatment, despite all the difficulties with compliance. Lifestyle first !*

*Will delaying treatment until adulthood reduce effectiveness?*

*I abstracted this article in part to ask: What is the optimum age to begin screening? There is no standard age to begin primary prevention. It depends on the individual's risk profile. Not all patients have the same risk. Higher risk of CVD may be estimated by family history and simple clinical markers. Screening and treatment may be appropriate for young persons with a strong family history of early onset CVD (eg, familial hypercholesterolemia). Statin treatment may be reasonable in this group. I would start young persons at half-dose statin.*

*Long-term compliance with drugs and lifestyles in children and their families would likely be difficult. It would require frequent follow-up, which would be bothersome, costly, and resisted by the child.*

## **END OF LIFE CONVERSATION**

***Patient Autonomy Is Not Synonymous With Endless Choice. Shifting All The Burden To The Patient Or Family Is Not Patient-Centered Care At All.***

### **5-1 FREEDOM FROM THE TYRANNY OF CHOICE—TEACHING THE END-OF-LIFE CONVERSATION**

Thirty years ago, an intern had a conversation with a patient he still regrets to this day. The patient, a young man with widely metastatic lymphoma, unresponsive to chemotherapy, now had progressive dyspnea. The internist knew that, even with intubation, his patient would soon die. The norm at that time was for physicians to make end-of-life (**e-o-l**) decisions without involving the patient. The medical team, struck by the patient's youth, asked the intern to elicit the patient's wishes. Uncertain, and frightened, the patient said "I want everything". Intubation followed, and then multi-organ failure. The patient died on the ventilator weeks later, never getting an opportunity to say goodbye to those he loved.

More recently another resident made a decision he feared he would regret. A woman in her 30s with widely metastatic breast cancer presented with shortness of breath due to bilateral malignant effusions. His job was to triage the patient to the proper level of care. Although her cancer had been diagnosed a decade earlier, no physician had discussed her e-o-l wishes. In the middle of the night, the patient was in respiratory extremis. Intubation was necessary if her life was to be prolonged. The resident decided to make it clear that she was dying. Comfort measures were initiated. The resident

feared he had overstepped his bounds and that the patient's oncologist would be angry. Instead, when the patient died peacefully 3 days later, the oncologist and the family expressed their gratitude.

In the 3 decades between these 2 experiences, the typical approach to discussing resuscitation has evolved from paternalism to discussions in which the patient and family are often asked to choose from a bewildering array of medical possibilities. To rectify perceived violation of patients' autonomy, healthcare institutions now require physicians to involve patients and families in e-o-l decisions. But physicians may lack the required trainees to lead such conversations confidently and effectively. A recent survey of internal medicine residents reported that they were frequently asked to lead such conversations, but only a third felt comfortable doing so.

Miscommunications may occur. When patients request "Do not resuscitate", such orders may not be placed in the medical record. They may be disregarded. In other cases, patients may not recall ever having such a conversation

Conversations with patients and families may focus on specific interventions rather than on the overarching goals of care. "Do you want us to pound on your chest if you need it?" "Do you still want antibiotics?" "Do you want intravenous fluids administered?" This ignores the fact that most patients and families have no basis on which to make such decisions. Patient autonomy is not synonymous with endless choice.

This impulse to offer patients a menu of options reflects fundamental insecurity about ability to prognosticate. Who are we to know when a patient will die?

Trainees are often the first initiators of e-o-l conversations. A survey of 2500 patients with metastatic cancer reported that only 20% of the patients' oncologists had documented their patients' code status.

We do not have suitable guidelines about e-o-l conversations. Experts suggest that these conversations should clarify prognosis and end with the physician's recommendations. This approach is not widely disseminated to trainees. And may even be rare in attending physicians.

Despite the current push toward patient-centered care, when it comes to the e-o-l, some patients and families prefer more physician-driven decision-making. In one study of seriously ill hospitalized patients, only 16% wanted to make treatment decisions alone. Shifting all the burden to the patient or family is not patient-centered care at all.

End of life conversations should be treated like any other competency. Every individual admission of a seriously ill patient should include an assessment of prognosis.

Leading conversations about e-o-l requires skills that are difficult to teach. There is a tendency to shy away from death. Conversations should include the words “death” and dying”.

These conversations will not get easier. The population is aging. Hospitalists have assumed care that would once have been followed by primary care physician. Long work hours erode relationships with patients. With medical advances, there is almost always something else that could be offered.

“A physician who merely spreads an array of vendibles in front of the patient and then says ‘Go ahead and choose it’s your life’ . . . does not warrant the somewhat tarnished, but still distinguished title of doctor.”<sup>1</sup>

NEJM May 3 2012; 266: 1655-57 “Perspective” first author Daniela Lamas, editorial fellow at NEJM  
1 Statement from Franz Ingelfinger, former editor of NEJM , who died of esophageal cancer, published posthumously in the journal.

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*There would have been ample time and opportunity for discussions of e-o-l concerns of the two patients described in the anecdotes. In both instances, the attending physicians left the responsibility to residents when the patients were dying. This responsibility should not be transferred.*

*The article is slanted to academic medical centers in which residents are being trained. Primary care clinicians do not usually have this advantage They have to plan ahead and act alone. They must practice the art of communicating about death.*

*I believe decisions about interventions when patients are approaching death depend on this judgment: What will this patient’s life be like if death is postponed and the patient regains her previous status? What will this patient look forward to if life is prolonged? Prognosis should not be limited only to the short term. Would the patient choose a longer life of complete dependence and dementia?*

*“Hope springs eternal”. But we can often be sure than there is no hope for survival or improvement. This does not mean that there is nothing left to do for patient and family. They should not be abandoned.*

*Death is one of the two most important episodes in life. And is the one for which we may make plans. Primary care clinicians may shy away from these discussions for lack of a perceived opportunity. There may be a helpful introduction—simply ask the patient “Are you at peace?”, and proceed from there. This can permit discussions at a time when stress is not so great.*

*Confused communications are common. Communications must be repeated. The wishes of a patient in a nursing home may be overlooked in the confusion of sudden collapse. The patient meanwhile may have lost the ability to communicate his wishes. There are times when patients may wish to change a decision temporarily –e.g. when a family wedding or graduation is approaching.*

*Most patients die in institutions. Most would rather die at home. Do not delay calling for help from Palliative Care and Hospice. Often their aid is requested at the last moments. They may help the patient to stay at home and support the family to care for the dying patient. Chaplains and clergy can be very helpful.*

*There are cultural differences which primary care clinicians should consider. Not too many decades ago, in some ethnicities, it was the norm to avoid mentioning the word “cancer”. This was considered to indicate loss of hope. Fortunately, times have changed, and I believe most Americans are becoming more comfortable with contemplating death.*

*Some interventions at the time of death may be considered to be cruel. Although patients and families may refuse interventions, they may not demand them if they are not considered appropriate or indicated. Physicians can refuse to intervene. They may do so indirectly as when responding very slowly to an emergency call for resuscitation.*

*The message is—plan ahead. Be prepared for the second most important event of your life,*

## **FAMILY HISTORY**

### ***Identifies Higher Risk***

#### **2-5 EFFECT OF ADDING SYSTEMATIC FAMILY HISTORY ENQUIRY TO CARDIOVASCULAR DISEASE RISK ASSESSMENT IN PRIMARY CARE**

Family history (FH) is a recognized risk factor for many chronic diseases. It is traditionally a part of history-taking in practice.

Guidelines for risk assessment of CHD are based on the Framingham risk-factor assessment and are widely used in the UK. It incorporates age, sex, smoking, systolic BP, and the ratio of total to HDL-cholesterol.

The trial asked: If such information is collected and used systematically, how many more persons at high risk would be identified?

This trial compared 1) an intervention in which FH of premature CHD was systematically collected

and incorporated into risk assessment [intervention group] with 2) risk assessment based on usual practice [control group]. Included 24 matched family practices in England (2007-2000; total of 748 patients; age 30-65).

Patients in 12 practices (control group) received the Framingham-based cardiovascular risk assessment using existing FH information in their electronic medical record.

Patients in 12 practices (intervention group) in addition completed a more detailed questionnaire to systematically collect the FH, which included a FH of premature CHD. Identified 105 (15%) patients as having high risk based on FH.

For participants in the intervention group, the percentage of those at high risk increased by 5.1%. In the control group (which considered only the FH initially incorporated in the electronic health record) risk increased by 0.5%. (Difference = 4.6%)

The number of participants at high risk in the intervention group increased from 49 to 69 (40%) after the FH from the questionnaire was incorporated.

About 5% in both groups had a positive FH of CHD in the original electronic record. This increased to 29% in the intervention group.

Annals Internal Medicine February 21, 2012; 156: 253-62 Original investigation, first author Nadeem Qureshi, University of Nottingham, UK

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*The venerable FH has largely been neglected in favor of other markers of risk. I am delighted to see it resurrected. FH is important.*

*FH is easily ascertained by self-reporting for inclusion in the electronic record.*

*After obtaining the FH and including it in the risk profile, what next? It should lead patients to better their lifestyles and take appropriate drugs as needed. This may be surprisingly unsuccessful.*

*The Surgeon General's Family History Portrait tool is available on line. It helps patients to complete a detailed FH for personal use and for the medical record.*

## **HORMONE REPLACEMENT THERAPY**

### **2-3 HORMONE REPLACEMENT THERAPY**

Hormone replacement therapy (**HRT**) contains estrogen-alone (**E**) for relief of menopausal symptoms (in women who have had a hysterectomy) and estrogen combined with progesterone (**E +P**) in those with an intact uterus—to protect against endometrial cancer.

Vasomotor symptoms are normal and affect about 80% of women during the menopause transition. Symptoms are severe in 20%. Median duration is 4 years, but symptoms may persist for years. HRT is indicated when symptoms adversely affect quality-of-life.

HRT is the most effective treatment for vasomotor symptoms. It also reduces fracture risk; improves vaginal dryness and sexual function; and may also improve muscle aches and pains.

### Adverse effects of HRT:

**Breast cancer:** E + P increases risk. It also increases breast density and the likelihood of having a difficult-to-read mammogram. For E-alone data are conflicting. The Women's Health Study and the Million Women Study reported increased risk for use for 5 to 7 years. Most observational studies report no increased risk. Studies show the greatest risk is related to E + P.

**Venous Thromboembolism:** Both E-alone and E + P increase risk of VTE and pulmonary embolism. The risk increases with age and other risk factors such as obesity, previous VTE, smoking and immobility. Previous VTE is a contraindication. Compared with oral HRT, transdermal HRT may lessen risk of VTE. In low-risk patients, low dose estrogen may not increase risk.

**Stroke:** HRT (both E-alone and E + P) increases risk of stroke. Risk rises with age, and duration of HRT use. Risk is lowered by use of transdermal preparations.

**Cholecystitis:** Large trials have shown increased risk of cholecystitis.

**Coronary heart disease:** Relationship between HRT and CHD is controversial. Risk increases with age, duration of use of HRT, and pre-existing CHD. In women under age 60, there is no statistically significant risk. In older women, HRT is generally avoided. Because they are more likely to have CHD.

**Endometrial cancer:** E-alone may lead to endometrial hyperplasia and increased risk of cancer. E + P does not increase risk. E-alone should not be used in patients who retain their uterus,

### Avoid or discontinue HRT:

- Uncontrolled hypertension

- History of breast cancer. (Check mammography results before starting)

- Known or high risk of VTE, stroke, CHD,

- Abnormal liver function. (HRT are metabolized by the liver)

- Abnormal vaginal bleeding

- History of endometrial or ovarian cancer

- History or high risk of gallbladder disease

Other considerations:

Start with a low dose and gradually increase dose as needed to control symptoms. Use HRT at the lowest dose for the shortest time. Care in starting long after menopause. .

Background disease and risks of HRT increase with age.

Consider HRT in patients at high risk of fracture.

Consider associated depression and anxiety in women with severe menopausal symptoms.

Transdermal HRT is safer than oral .

Gabapentin (*Neurontin*; Pfizer; originally a drug to treat epilepsy—later used for neuropathic pain) is the only non-hormonal product to be equally effective as low dose estrogen for vasomotor symptoms.

BMJ February 25, 2012; 344: 44-49 “Practice” review article, first author Marin Hickey, University of Melbourne, Australia

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*Treatment of menopausal symptoms is an important application for primary care. It benefits many women.*

*In general, estrogen-alone is safer than combined estrogen-progesterone. I believe progesterone is the major contributor to the risk of breast cancer. Progesterone protects against endometrial cancer (when estrogen is used), but an important question is—Does the increase in breast cancer outweigh the reduction in endometrial cancer?*

*The term “hormone replacement therapy” is entrenched in medical terminology. But it is imprecise and confusing, and, I believe, obsolete. The term applies to estrogen-alone, progesterone-alone and the combination. They are completely different drugs. It also could be applied to other hormone replacements such as insulin, thyroxin, and cortisol. I believe the term should be abandoned and replaced by more specific hormonal drugs.*

*If used cautiously, E and E +P treatment of menopausal symptoms is safe.*

## **HYPERTENSION**

### **1-3 ANTI-HYPERTENSIVES IN OCTOGENARIANS**

A previous study in NEJM (2008)<sup>1</sup> examined whether initiating treatment of hypertension in patients over age 80 is beneficial.

Randomized 3845 subjects with a sustained systolic BP of 160 or over to: 1) Indapamide 1.5 mg sustained release (a diuretic) with added perindopril 2 or 4 mg (AC-inhibitor) if needed to reach target BP of 150/80, or 2) Placebos. By 2 years, 73% of the active group was taking both drugs

At baseline, mean age was 84; mean BP was 173/91; 12% had a history of cardiovascular disease; 65% were already taking anti-hypertension treatment; 33% had isolated systolic hypertension.

Participants were generally healthy.

At 2 years, mean BP in the treated group was 150/61. Target BP was reached in 50%. (Results may have been more favorable if more participants had reached target.)

Active treatment (compared with placebo) was associated with a 30% reduction in fatal; and non-fatal stroke; 39% reduction in rate of death from stroke; 21% reduction in death from cardiovascular disease (CVD); and 64% reduction in heart failure.

Main endpoints (intention –to-treat). Rate per 1000 person-years:

	Active	Placebo
All stroke	12	17
Fatal stroke	7	11
Any cause death	47	60
Any heart failure	5	15
Death from CVD	24	31
Any CVD event	34	51

In absolute terms, a reduction of 2 to 17 individuals per 1000 person-years.

Adverse events: Only 3 were classified as possibly due to placebo vs only 2 in the treatment group. Hypokalemia was very uncommon. The authors attributed this to the ameliorating effect on K loss when ACE inhibitors are added to diuretics.

The authors concluded that the target of 150/80 is beneficial .

The present study<sup>2</sup> is a one-year open-label extension of the original study. Both the former active and placebo groups (n = 1712; 788 previously taking placebo) were included.

Both groups received active treatment. The drug program was the same. Target BP was again titrated to 150/80.

Determined cardiovascular events during the year. Endpoints remained the same.

At 6 months, there was no statistical difference in BP between the two previous groups. (Mean BP 145/76)

No serious adverse effects were reported in the former two groups.

Main outcomes per 1000 person-years during the 3<sup>rd</sup> year. (Intention to treat):

Endpoint	Previous placebo	Previous active treatment
All stroke	5	10
All cause mortality	39	19
CVD mortality	12	2
Heart failure	17	1
All CVD events	17	13

(The benefits in the 2-year treated group were carried over in the 3<sup>rd</sup> year. The previous placebo-treatment group seemed to benefit.)

During the follow-up year, (1682 patient-years) 47 patients died. There were no statistically significant differences between the groups in rate of stroke, CVD events, and heart failure. There were significant differences in total mortality and CVD mortality. (Favoring those treated during the preceding 2 years.)

No serious adverse effects were reported.

1 Treatment Of Hypertension In Patients 80 Years Of Age And Older NEJM May 1, 2008; 358: 1887-98 by the Hypertension in the Very Elderly Trial (HYVET), first author Nigel S Beckett, Imperial College, London.

2 Immediate And Late Benefits Of Treating Very Elderly People With Hypertension: Results From Active Treatment Extension To The HYVET first author Nigel S Beckett, Imperial College, Lond

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*Is it ethical to discontinue anti-hypertension treatment in patients with established hypertension?*

*The studies were of short duration and with relatively few patients. Nevertheless, I believe the studies carry an important message. The benefits of treatment could easily be applied to patients in their 60s, 70s and even 90s.*

*These patients were "in reasonably good health for their age". . Treatment of frail, older patients would require more consideration.*

*I believe hypokalemia would be more common in primary care practice. Would it be reasonable to start patients on the 2 drugs? The authors state that ACE inhibitor may have lessened the hypokalemic effect of the diuretics. I would start these patients on half dose.*

*Authors and editors persist in reporting benefits as percentage reductions, hazard ratios, and relative risks. In my view, this can be outrageous “spin” and is very misleading, especially to patients. The “64% reduction in heart failure” was, in absolute terms, a reduction from 15 individuals to 5 individuals per 1000 person-years—a benefit of one in one hundred.*

## **HYPERTHYROIDISM**

*Associated With An Increased Risk Of Total Mortality, CHD Mortality, And AF*

### **5-3 SUBCLINICAL HYPERTHYROIDISM AND THE RISK OF CORONARY HEART DISEASE AND MORTALITY**

Subclinical hyper-thyroidism (**sc-hyper-t**) is defined by a low thyrotropin (**TSH**) level and normal concentrations of free thyroxine (**FT4**) and triiodothyronine (**T3**).

This study included individual data on 52 674 participants pooled from 10 cohorts. Median age= 59; 58% women; median duration of follow-up = 8.8 years. Defined sc-hyper-t as a second generation, more accurate, TSH level lower than 0.45 mIU/L with normal FT4 levels; euthyroidism as TSH between 0.45 and 4.49.

Sc-hyper-t was further categorized as levels of TSH below 0.10, and levels of 0.10 to 0.44. This included 1884 (3.6%) with TSH (0.10 to 0.44) and 304 (0.15%) with TSH <0.10.

Risks (hazard ratios [**HR**]) were consistently greater in the sc-hyper-t groups. However, absolute risks were small. Stroke and cancer mortality did not differ.

	HR for sc-hyper-t vs euthyroid	Risks per 1000-person-years
Total mortality	1.24	+3.6
CHD mortality	1.29	+0.6
CHD events	1.21	+3.2
Incident AF <sup>a</sup>	1.68	+4.6

(a atrial fibrillation)

CHD events and incident AF (but not other outcomes) were significantly greater in those with lower TSH levels

A. TSH 0.10 to 0.44	HR	
	CHD mortality	Incident AF
	1.24	1.63
B. TSH lower than 0.10	1,84	2.54

The population-attributable risk was 0.7% for total mortality, and 6.2% for incident AF.

Recent guidelines suggest that treatment of sc-hyper-t should be strongly considered in all individuals age 65 and older with TSH levels below 0.10. And treatment should be considered in individuals age 65 and over with TSH levels 0.10 to 0.44.

Conclusion: Endogenous sc-hyper-t is associated with an increased risk of total mortality, CHD mortality, and AF, with higher risks in those with TSH levels below 0.10 mIU/L. The study is observational and cannot assess whether the risks associated with sc-hyper-t are lowered by treatment.

Archives Internal Medicine May 2, 2012; first author Tinh-Hai, University of Lausanne, Switzerland

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*This is not a strong study. I believe their estimate of prevalence of sc-hyper-t is too high. There is doubt about application of the data to younger patients.*

*There is a distinction between screening and testing, which I believe should be preserved. Screening applies to performance of a test for a disease or condition for which the patient has no symptoms or signs. Screening the general population for sc-hyper-t is discouraged. Testing applies to patients who have signs or symptoms of a disease of interest.*

*TSH screening has an advantage in that it will diagnose hypo-thyroidism as well.*

*The prevalence of sc-hyper-t is low, and, if diagnosed, treatment, in absolute terms, yields relatively few benefits. We should focus on those who are at higher risk: eg, with nervousness, fatigue, weakness, heat intolerance, palpitations, new onset AF, supraventricular tachycardia, unexplained weight loss, fatigue, and signs such as thyroid enlargement, and thyroid nodules, use of causative medications, and older women with osteoporosis. Indeed screening may be more effective in women older than 50 because 1 of every 71 has unsuspected sc-hyper-t or overt hyperthyroidism.*

*The term apathetic hyperthyroidism applies to those with fatigue, depression, weight loss, and AF.*

*Thyroid disease is common. Prevalence in the US is estimated to be about 1%; 40% overt and 60% subclinical. Primary care clinicians, usually the first to encounter these patients, should be constantly aware.*

*The reference range of TSH has been disputed and changed over the years, depending on the technique and the laboratory. In 2004 the SI units defined the range as 0.5 to 4.7 mIU/L, My local laboratory defines it as 0.3 to 3.0. Certainly, the lower the TSH, the more likely is sc-hyper-t.*

*The distinction between exogenous hyperthyroidism and endogenous hyperthyroidism is important. Exogenous hyper-t may occur when the dose of therapeutic levothyroxin is too high or when patients take it surreptitiously.*

*I would not hasten to treat sc-hyper-t. Many patients are asymptomatic, or have mild symptoms. There is substantial disagreement about how and when to treat. TSH levels may return to normal without treatment. Those with TSH < 0.10 and those with convincing symptoms should be treated. Clinical judgment is required.*

*(Some of these editorial comments were based on an excellent review in the July 3 2012 issue of the Annals of Internal Medicine. Written by Michael T McDermott. )*

#### **5-4 WHAT IS THE IMPORTANCE OF SUBCLINICAL HYPER-THYROIDISM?**

*(This commentary expands on the previous article. Ed. )*

Subclinical hyper-thyroidism (**sc-hyper-t**) is defined as having a normal free thyroxine (FT4) and a normal total triiodothyronine (T3) in conjunction with a thyrotropin (TSH) level persistently below the reference range, in the absence of factors known to suppress TSH.

Factors that may alter thyroid function tests include medications (eg, corticosteroids, dopamine), pituitary and hypothalamic dysfunction and non-thyroid illness—a wide variety of illnesses that can alter thyroid function tests.

In general, the diagnosis of sc-hyper-t is made in ambulatory outpatients who are not taking medications known to affect thyroid function. The most common causes include Graves disease (usually younger patients), multi-nodular goiter (usually older patients) and solitary autonomous thyroid nodules.

The incidence of sc-hyper-t in the population is about 1%.

The distinction between endogenous and exogenous disease is important since exogenous sc-hyper-t can be treated by modulating the levo-thyroxine dose.

In addition to adverse cardiovascular (CVD) effects, sc-hyper-t is associated with risk of osteoporosis.

The main conclusion of the preceding study was that sc-hyper-t is associated with increased mortality and AF regardless of age, sex, and previous CVD. There was a trend for increased risk if TSH was lower than 0.10 mIU/ L.

Given the potential adverse effects of sc-hyper-t, how should primary care clinicians respond?

The editorialists suggest considering tests to assess possible causes:

Complete history and physical exam

Thyroid ultrasound

Radioactive iodine uptake and scan

Bone mineral density

Electrocardiography

Comprehensive metabolic package

Repeat TSH, FT4, T3

Thyroid antibodies

Thyroid stimulating immune globulin

Prior to treatment, guidelines suggest repeating the thyroid function tests at 3 and 6 months to confirm stability. Sc-hyper-t may not be persistent. TSH levels may return to normal, or rarely progress to overt hyperthyroidism (~1%).

Once sc-hyper-t has been established, and external causes are considered (eg, medications, systemic illness), the most salient issue is whether to treat, and by what modality.

Recent guidelines indicate:

When TSH is persistently less than 0.1 mIU/L treatment should be strongly considered in an individual age 65 and older and in postmenopausal women who are not on estrogen or bisphosphonates; in patients with CVD risk factors; heart disease; osteoporosis; and individuals with hyperthyroid symptoms.

When TSH is persistently below the lower limits of normal, but over 0.10 mIU/L, treatment should be considered in individuals age 65 and older and in patients with heart disease or osteoporosis.

Treatment modalities and underlying principles of treatment are compatible with overt hyperthyroidism, including anti-thyroid drugs, radioactive iodine, and surgery. Methimazole is the first-line drug (compared with prophythiuracil) except during the first trimester of pregnancy. However, it is often difficult to formulate the optimum approach. Sc-hyper-t is usually milder than overt hyperthyroidism and may be controlled with lower doses of methimazole. Patients may be reluctant to accept surgery or radio-iodine therapy when the disease is mild and the patient asymptomatic. Older patients are usually treated with low doses of methimazole with periodic monitoring.

The preceding study provided information regarding the importance of recognizing sc-hyper-t. Until more information is available, the relationship between sc-hyper-t and total- mortality, CVD- mortality, and AF presently provides sufficient evidence to consider treatment, especially in patients with CVD risks, hyperthyroidism or osteoporosis.

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*While writing abstracts on sc-hyper-t and sc-hypo-t (Practical Pointers March 2012) I began to think how much primary care practice these days depends on laboratory and imaging reports. We order screening packages routinely, sometimes without much thought about the risk of underlying disease. And without any knowledge and consent by the patient.*

*As a result, patients are entered into the medical “system”. The system goes on to more and more tests and consultations, with increasing costs, inconvenience and anxiety. We rely less on patient symptoms and concerns. We examine the patient less frequently.*

*Sc-hyper-t is a good example. A “routine” blood test suggests something amiss. More and more tests are ordered even though the patient feels well and has no suggestive symptoms or signs of the disorder. We follow the lab reports, not the patients. Would it not be better to simply follow the patient in the old-fashioned clinical way—continuing history and physical examinations. Little harm will be done in delaying the diagnosis.*

*Screening tests do indeed have a place in medical practice. They should be applied judiciously. There is a downside.*

## **HYPOTHYROIDISM**

***At Present, Clinicians Will Need To Rely On Their Clinical Judgment And Well-Meaning, But Necessarily Vague Clinical Practice Guidelines And Expert Opinion.***

### **3-3 SUBCLINICAL HYPOTHYROIDISM**

“Subclinical” denotes the presence of a disease without obvious symptoms—an early stage of evolution of a disease. Subclinical hypothyroidism (**SCHOT**) occurs when thyroid stimulating hormone (**TSH**) is high and free thyroxin (**T4**) and T3 levels remain within the normal reference range.

Diagnosis is based on the exquisite sensitivity of the hypothalamic-pituitary- thyroid axis. Serum TSH changes logarithmically. Free T4 changes arithmetically. Therefore changes in free T4 that are within the normal range will cause increases or decreases in TSH that are likely to be outside the reference range. Most experts agree that SCHOT represents early mild thyroid failure. Depending on

the size of the increase in serum TSH it can be mild (TSH 4.5-9 mU/L), or severe (TSH 10 mU/L and over). Most patients with SCHOT have the mild form.

Transient increases in SCHOT may occur. The TSH level should be repeated in 3-6 months to rule out laboratory error and a transient increase.

Antithyroid antibodies, a marker of chronic autoimmune lymphocytic thyroiditis (Hashimoto) are present in 60% to 80% of persons with elevated TSH. High antithyroid autoantibody titers are associated with persistent raised serum TSH.

The NHANES III study reported 4% of the US population had SCHOT. Overall incidence increases with age and in females.

Although dyslipidemia (especially elevated total- and LDL-cholesterol) is associated with overt hypothyroidism, the relationship with SCHOT is controversial. The association may be stronger in patients with TSH levels above 10 mU/L.

Maternal SCHOT can lead to serious obstetric complications including increased risk of miscarriage, placental abruption, low birth weight, and premature delivery. Impaired mental function has been reported in children born of inadequately treated women with SCHOT.

Generally, treatment does not improve mood, cognition, or symptoms unless the TSH is more than 10. In a meta-analysis of 13 studies of levothyroxin therapy, the effects of therapy were proportional to both the severity of SCHOT and the increase in serum lipids. Both total- and LDL-cholesterol were modestly reduced.

Population screening (of asymptomatic patients) is controversial because the benefits of treatment are unproven for most individuals who might be diagnosed through screening programs.

Conclusion: SCHOT is common in clinical practice. Since most patients are asymptomatic, screening is the only way that most patients will be identified. Yet, experts do not agree about whether screening is worthwhile because no large population-based randomized, controlled trials show that intervention is beneficial. The data are sufficient, however, to recommend treatment of patients who are over age 65, and have TSH levels of 10 and over. Treatment can also be recommended for pregnant women with TSH levels above the reference range for pregnancy. For most patients with TSH concentrations between 5.0-10, no firm recommendations can be made. The decision to treat will be made on various clinical factors. At present, clinicians will need to rely on their clinical judgment and well-meaning, but necessarily vague clinical practice guidelines and expert opinion.

Lancet March 24, 2012; 379: 1142-54 Seminar, first author David Cooper, Johns Hopkins School of Medicine. Baltimore MD.

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*I abstracted this article in detail and at length because I knew little about SCHOT and considered it an important clinical application. World-wide, thyroid disease is becoming epidemic.*

*One word describes the state of our knowledge about SCHOT—“uncertainty”.*

*At present, decisions about screening and treatment rely on clinical judgment. Pay attention to new or unusual symptoms. Increased suspicion related to pregnancy is warranted.*

*I believe many primary care clinicians screen frequently.*

*Should we screen for antithyroid antibodies? I do not believe it will aid decisions about treatment in primary care practice. Routine screening will exceed our efforts to practice good stewardship of medical interventions and costs.*

*A  $n = 1$  trial may be helpful. Try a short time of low dose levothyroxin. Are symptoms improved? Do symptoms improve as well on a placebo? A short course of low-dose levothyroxin is likely harmless. Carefully follow-up for effect on symptoms and TSH.*

*My laboratory cites a reference range for TSH of 0.30 to 3.0.*

*The article also includes discussion of subclinical hyperthyroidism, equally interesting. I omit this.*

## **PATIENT CARE**

***Patients Have A Right To Understand The Options Available And To Be Supported To Make The Decision That Is Right For Them.***

### **4-1 PUTTING PATIENTS FIRST**

A guideline from NICE (the UK National Institute for Health and Clinical Excellence) aims to create sustainable changes that will result in a cultural shift toward a patient –centered service. It places the principle of a high quality patient experience at the heart of good clinical care. When implemented, the recommendations will lead to feasible and effective improvements in care.

However, much of the guideline states the obvious. Many challenges remain in providing a health service that systematically, reliably, and demonstrably puts patients first.

It is a sad indictment of modern health care that we need such guidance in the first place. Most people would expect that delivering good service would be secondary nature to the “caring profession”. Sadly, evidence suggests that this is not the case. The reality is that people who work in health care often seem to be immune to patient’s anxiety, excessive waiting, and unnecessarily

distressing experiences. Almost every day they walk past, or participate in, care that is not delivering a good experience.

Improvements will not be seen until we understand and improve the attitudes and behaviors of health professionals as well as the systems and structures of care.

The definition of patient experience is limited by our inability to see into the lives of those we cared for.

The most important challenges are long-term conditions, aging, and multi-morbidity—the conditions patients live with. These consume about 70% of health and social care. A much broader definition of “patient experience” includes the experiences patients have every day, and not just the health care they receive. Self management is already default care for people living with long-term conditions. If the experience of patients who self-manage is to be improved, they must be recognized as active co-producers of their own health. They should be supported in developing the knowledge and skills to become confident self-managers of their own conditions.

All interventions to support self-management have a positive effect on clinical symptoms and outcomes, attitudes and behaviors, and quality of life. That such approaches are not the norm is one of the greatest failures of modern medicine.

Support for self management has a theoretical basis within health psychology, which profoundly distinguishes it from more didactic patient education and information provision.

NICE guidelines too often reinforce the myth of the “right way” to deliver care, at the risk of ignoring the principle of shared decision making. Patients have a right to understand the options available and to be supported to make the decision that is right for them.

BMJ April 7, 2012; 344:11 Editorial, first author Simon Eaton, Northumbrian Health Care, North Shields, UK . BMJ2012; 344:e2006

This editorial is linked to “Improving the Experience of Care for People using NHS Services: A summary of NICE guidelines”, first author Norman O’Flynn, Royal College of Physicians, London, UK BMH2012;344;D6422

The emphasis of health care has often been on clinical care and outcomes, which can come at the expense of patients’ experiences. Giving attention to the individual has become more difficult as healthcare has become more technical and specialized, involving more people and services. Patients have less opportunity to develop relationships with the professionals who treat them. They are more likely to be treated by a team.

The National Health Service recognized the experience of patients as one of 3 dimensions of quality. The other 2 are clinical effectiveness and safety.

The article summarizes the most recent recommendations on improving patients' general experience of care. The recommendations cover mainly the interaction between healthcare staff and patients.

Recommendations for healthcare professionals:

- Know the patient as an individual
- Tailor healthcare services to the individual
- Ensure continuity of care and relationships
- Enable active participation of the patient in their care

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*There are 2 parts to every consultation: the disease, and the patient with the disease.*

*I have had my share of triumphs and tragedies over the years of active practice as a primary care internist. Looking back, I almost always focused on the disease. I would have been a better clinician if I had been more aware of the patient's beliefs and feelings, and willingness and ability to participate in their own care.*

*I would be more willing to say at the end of the initial consultation—"Now tell me about yourself". The goal is to try to know the patients as one would know a family member or a good friend. This takes time. We must save some time for it.*

*Getting to know the patient as a person is a remit of primary care. We have the privilege of following patients over years, and afterwards attending to their children. Specialists who consult with the patient for only one episode of medical illness or surgery lack this opportunity. It takes time to establish an enduring relationship. Our early forebears in medicine relied mainly on kindness, presence, and attention for therapy. That was all they had to offer.*

*The article's focus on self-management is important. One of our greatest challenges is to convince patients to care for their own health. Success is infrequent. Keep trying. We must try to understand why a patient continues to smoke, abuse alcohol, lead a sedentary life, and will not follow a more healthy diet. Be aware, however, that some patients are economically unable to do all of this.*

*Caring for the patient is not a new imperative. What is new? More emphasis on involving the patient in decision making and encouraging them to take more responsibility for their health. If cure is not possible, provide comfort and encourage the patient to accept what cannot be changed.*

*Francis Peabody's famous aphorism bears repeating; "The secret of the care of the patient is the caring for the patient".*

***Do The Right Thing For The Patient—Make Health Care More Patient-Centered***

**6-1 GOAL-ORIENTED PATIENT CARE: An Alternative Health Outcome Paradigm**

The Center for Medicare and Medicaid Services has launched major efforts to make care more patient-centered, defined as “respectful of, and responsive to, individual patient needs, and values, and ensuring that patient values guide all clinical decisions”.

At present, measures of quality address preventive and disease-specific care processes (eg, smoking cessation counseling and initiation of appropriate medications after myocardial infarction). The focus has been on condition-specific indicators, both short-term (HbA1c levels and hypertension control) and longer-term (disease-free survival) as well as overall motility. These process and outcome measures work well for relatively healthy patients with a single disease. They may be inappropriate for patients with multiple conditions, severe disability, or short life-expectancy. For such patients, the overall quality of care depends on more than disease-specific care processes. It should be considered in the context of the individual patient’s goals and preferences.

An alternative approach to providing better care would be to focus on patient’s individual health goals within a variety of dimensions (eg, symptoms; physical functional status; and social functioning) and determining how well these goals are being met.

The goal-oriented approach to making health care decisions, assessing outcomes, and measuring success has several advantages:

- 1) Frames the discussion in terms of individually desired rather than universally applied health status. For example, a new therapy may extend life for a patient with metastatic prostate cancer for several months. But the patient may not perceive this small gain as worthwhile.
- 2) Simplifies decision making for patients with multiple conditions by focusing on outcomes that span conditions, and aligning treatment toward common goals. Choices to deescalate treatment for one condition in order to optimize treatment for another can be made in the context of whatever therapy is most likely to achieve the patient’s goals. Success or failure in attaining these individualized outcomes is easily determined. It is feasible to use goal attainment to assess treatment effectiveness and quality of care for patients with multiple clinical conditions. Multiple potential competing disease-specific outcomes can be replaced by ascertaining whether individual health goals were elicited and attained.
- 3) Prompts patients to articulate which health states are important to them, and their relative priorities. Patients can be in control when treatment options require trade-offs (eg, better symptom control at the expense of potentially shortening life span). Such trade-offs are currently being made (eg, when patients choose to receive hospice care and decline aggressive treatment).

4) Allows for effective shared decision-making, with the patient selecting the health outcome of highest priority and the clinician determining what treatment strategies are most likely to achieve that outcome.

Not all patient goals may be realistically attainable. A patient with a dense hemorrhagic stroke may not be able to live alone even if doing so is a major personal goal. Clinicians need to explain what is possible and negotiate potentially achievable goals with the patient. The clinician should then provide a treatment plan, encouragement, and advocacy to meet the agreed goals. And readdress them if the situation changes over time.

Some goal decisions may be associated with adverse effects (eg, a family of a patient with dementia who has behavioral problems may elect to use an antipsychotic drug, in spite of the increased risk of death from CVD, because the drug controls behavior well enough to allow the patient to remain at home). In such a case, a positive outcome from the perspective of the individual could contribute negatively to the perceived quality of the clinician's care.

The most important barrier to goal-oriented care in medicine is the deep-rooted disease- outcome based paradigm. Rather than asking what patients want, the culture has valued managing each disease as well as possible according to guidelines.

Ultimately, good medicine is about doing the right thing for the patient. For patients with multiple diseases, severe disability, or limited life-expectancy, any accounting of how well we are succeeding in providing care must above all consider the patient's preferred outcomes.

NEJM March 1, 2012; 366: 777-79 "Perspective", first author David B Reuben, David Geffen School of Medicine, UCLA, Los Angeles

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*As the editorials suggest, goal oriented patient care is a high expression of autonomy and beneficence.*

*Some elderly patients may not be aware that they have a choice. They may simply rely on the doctor's advice. Clinicians should make it clear that they do have a choice, and may suggest a goal.*

*Our present practice, treating symptoms and diseases, leads to extreme polypharmacy, a result of the clinician's habit of automatically reaching for the prescription pad.*

*Some patients take 10 or 12 different drugs, leading to a complex daily routine or utter confusion. There is absolutely no way that benefit or harm can be ascertained from such a mixture. We do know that costs will be high.*

*The editorial focuses on the patient. Dealing with families maybe entirely different. Again, be sure your patient has designated a valid power of health-care power of attorney.*

*End-of-life presents special opportunities for goal-oriented patient care. Most would rather die at home. During the last few months of life, hospitalization is often associated with intrusive tests and interventions. Compassionate clinicians may suggest to the family that home care is a goal and help facilitate it.*

## **RED MEAT CONSUMPTION**

### ***Associated With A Significantly Elevated Risk Of Mortality***

#### **4-3 RED MEAT CONSUMPTION AND MORTALITY**

This study investigated the association between red meat (**RM**) and cause-specific and total-mortality reported by 2 large cohorts.

Analyzed data from 2 prospective cohort studies: 1) the Health Professionals Follow-up Study (**HPFS**; 1986-2008; n = 37 698 men) and 2) the Nurses Health Study (**NHS**; 1980-2008; n = 83 644 women). At baseline, none had a history of cancer or CVD.

Unprocessed RM included beef, pork, or lamb as a main dish. The standard serving size was 3 oz. Processed RM included bacon (2 slices) one hot dog, and sausage, salami, bologna, and other processed meat (1 piece-28 g).

Baseline characteristics of participants according to quintiles of total-RM consumption:

	Total RM intake by quintile				
A. Men (Mean age 52)	1	2	3	4	5
RM mean servings / day	0.22	0.62	1.01	1.47	2.36
B. Women (mean age 46)					
RM mean servings / day	0.53	1.04	1.52	2.07	3.10

Lowest intake was 1 to 2 servings per week; highest more than 21 servings per week.

Every 4 years, updated the association between RM consumption and cause-specific and all-cause mortality.

Higher intake of RM was associated with a higher intake of energy, but lower intake of whole grains, fruit, and vegetables, poultry and fish.

For both cohorts combined, there were 23 926 deaths including 5910 CVD and 9464 cancer deaths during 2.9 million person-years of follow-up

Hazard ratios (HR) for mortality after multivariate adjustment for major lifestyle and dietary risk factors according to RM intake (quintiles):

	1	2	3	4	5	
All-cause mortality	1.00 <sup>a</sup>	1.10	1.15	1.21	1.30	a Referent
HR for mortality for 1-serving per day increase of total RM.						
Unprocessed RM	1.13					
Processed RM	1.20					

Unprocessed and processed RM intake were associated with an increased risk of total-, CVD-, and cancer-mortality. In the pooled analysis, for every one serving per day, mortality increased by 13% for un- processed RM, and 20% for processed RM.

Replacing 1 serving of RM with 1 serving of fish, poultry, nuts, legumes, low-fat dairy products, or whole grain was associated with a lower risk of total mortality: 7% for fish, 14% for poultry, 19% for nuts, 10% for legumes, 10% for low-fat dairy, and 14% for whole grains.

During follow-up an estimated 9.3% of total-deaths in men and 7.6% of deaths in women would have been prevented if participants consumed fewer than 0.5 servings per day of total RM.

Conclusion: Greater consumption of unprocessed and processed RM was associated with higher mortality risk. Compared with RM, other dietary components such as fish, poultry, nuts, legumes, low-fat dairy, and whole grains were associated with lower risk. Replacement of red meat with alternative healthy dietary components may lower the mortality risk.

Archives Internal Medicine April 9, 2012; 172: 55-63 Original investigation, first author Ann Pan, Harvard School of Public Health, Boston, Mass

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*Over the years, mortality was 23% higher in those who ate RM very frequently vs those who ate little.*

*I believe, this additional lifestyle intervention is an important public health application.*

*We are constantly reminded that, in observational studies, association does not prove causality. However, when the study is very large and long-term, it becomes more plausible..*

*High RM intake does not exist by itself. It is associated with lower intake of more healthy foods, which adds to risk.*

## RHINO SINUSITIS

*”Offered Little Clinical Benefit For Most Patients”*

### 2-4 AMOXICILLIN FOR ACUTE RHINO-SINUSITIS: A Randomized Controlled Trial.

Acute rhino-sinusitis (R-S) accounts for 1 in 5 prescriptions for antibiotics in adults in the US.

Evidence of efficacy is conflicting. This trial evaluated the incremental effect of amoxicillin treatment over symptomatic treatment in adult community dwellers on disease-specific quality-of-life in patients with clinically diagnosed acute R-S.

This randomized, placebo-controlled trial was conducted in 10 primary care offices. (2006-2009). Patients were adults age 18-70 (median age 32). All met the CDC’s diagnostic criteria for acute bacterial R-S. All had moderate, severe, or very severe symptoms.

Randomized (n = 166) to: 1) A 10-day course of amoxicillin 500 mg three times a day, or 2) Matching placebo three times a day. All reported purulent nasal discharge and maxillary pain or tenderness.

All patients received a 5 to 7 day supply of symptomatic treatments to be used as needed.

Primary outcome = effect of treatment on disease-specific quality-of-life at day 3.

The primary outcome was measured using the modified Sino-nasal Outcome Test -16. (SNOT-16), which considers both the severity and frequency of symptoms. Each participant scored how much each of 16 R-S related symptoms bothered them in the past few days—0 for no problem to 3 for severe problem.

Mean SNOT-16 scores

Day 0		Day 3		Day 7		Day 10	
A	C	A	C	A	C	A	C
1.71	1.70	1.12	1.14	0.65	0.84	0.48	0.49

(A = amoxicillin; C = control)

(For the SNOT-16 score, a difference of 0.5 is the minimal difference representing a clinically significant effect.)

The mean improvements in the SNOT-16 score was similar between groups except for day 7, when A was favored.

Eight patients stopped treatment at day 3; 13 at day 7; and 32 more by day 10. Reasons were failure to improve (2 in A; 6 in C); worsening symptoms (3 and 4); improved symptoms (4 in A); and adverse effects (1 in A). Sixteen were treated with another antibiotic. (5 in A; 11 in C)

Adverse effects: No serious adverse effect was reported in either group. Nausea, diarrhea,

abdominal pain, and vaginitis occurred equally (5% to 9%).

These findings support the recommendation to avoid routine antibiotic treatment for patients with uncomplicated acute rhino-sinusitis.

It is important to note that patients with symptoms indicative of serious complications were excluded from this trial, and likely to need a different strategy.

Conclusion: Treatment with amoxicillin for 10 days offered little clinical benefit for most patients with clinically diagnosed uncomplicated acute rhino-sinusitis

JAMA February 15, 2012; 307: 685-93 Original investigation, first author Jane M Garbutt.

Washington University, St. Louis, MO

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*I was unable to access the snot-16 score on Google. Apparently, it has been replaced by the SNOT-22. Both scores contain symptoms relating to the upper respiratory tract as well as systemic symptoms. They assess functional limitations, physical problems, and emotional consequences of rhino-sinusitis.*

*Patients request antibiotics to cure the infection. By “cure” they mean relief of symptoms. Symptomatic treatment, as applied in this study, relieves symptoms while the infection is cured by natural immunity. Many will improve in a few days. .*

*I believe treatment tilts slightly in favor of A. The greater improvement in the A group at day 7 may indicate some beneficial effect. In addition, a few more patients failed to improve in the C group and were given antibiotics. Some in the A groups discontinued treatment because of improved symptoms.*

*There will be some patients for whom antibiotics are required at the first visit because of the severity of the illness and the likelihood of complications from the sinusitis. Clinical judgment is required to distinguish this smaller group. Primary care clinicians may more readily prescribe antibiotics for this reason.*

*I believe the “if” or “delayed “ prescription is a useful approach to treatment by primary care clinicians. A prescription is written for the antibiotic, but the patient is admonished not to fill it unless symptoms get worse or do not improve over a few days. Most of the time, the prescription will not be filled.*

*There was no need for sinus X-rays.*

## SITTING TIME

### *A Risk Factor For All-Cause Mortality*

#### **3-2 SITTING TIME AND ALL-CAUSE MORTALITY RISK IN 227 497 AUSTRALIAN ADULTS**

This study focused on the dose-response relationship between total sitting time and all-cause mortality.

Over 220 000 participants, representing 11% of the population of a state of Australia, completed a baseline questionnaire (2006). All were over age 44.

Sitting time was assessed by asking: 1) About how many hours in each 24-hour day do you usually spend sitting?

Determined all-cause mortality (2006-2010) in relation to sitting time, adjusted for potential confounders. Daily sitting time (hours / day) was divided into 4 categories: 1) 0 to 3.9; 2) 4 to 7.9; 3) 8 to 10.9; and 4) 11 or more. Determined hazard ratios of all-cause death related to 0 to 3.9 hours per day.

During 621 695 person-years of observation (mean follow-up 2.8 years) 5405 deaths were registered.

Relationship between sitting and all-cause mortality after adjustment for sex, age, BMI, smoking, and other possible confounding factors:

Hazard ratios	Sitting time h/d			
	0-3.9	4.0 to 7.9	8.0 to 10.9	11 and over
All subjects	1.00*	1.02	1.15	1.40

\* Referent

The trend in the 4 groups showed a significant hazard ratio for all-cause mortality.

The population-attributable deaths due to sitting was 7%. Inactive participants with high levels of sitting had the highest mortality rate. “The results show that prolonged sitting is associated with higher all-cause mortality risk independent of physical activity.”

Sitting less than 8 hours per day, and meeting the physical activity recommendations of the WHO independently protected against all-cause mortality.

In the USA, less than half the adult population meets the WHO recommendations for physical activity. The potential public health gains of interventions to change activity are substantial.

Conclusion: Prolonged sitting was a risk factor for all-cause mortality, independent of physical activity.

Archives Internal Medicine March 26, 2012 Original investigation, first author Hide P van der Ploeg, University of Sydney, Australia

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*Practical Pointers has abstracted many articles demonstrating benefits of healthy lifestyles. This is a major responsibility and opportunity for primary care medicine.*

*The difficulty is: how to change patient-behaviors. This is difficult, but keep on trying.*

*We are a sitting society. A commentary attached to the full abstract suggested that incidental standing-walking around activity during the day, instead of sitting, would be beneficial. Physical activity does not require planning. Pretend you are on a cruise. Instead of sitting on a deck chair, walk around the deck. While waiting in an airport, don't sit, get up and walk around. When traveling to work in a car, park several blocks from the office. Keep active. Emulate the busy housewife.*

*This study has all the difficulties related to observational studies. Duration was less than 3 years—a short time. Longer duration may have demonstrated more differences between the groups.*

## **STATIN DRUGS**

**4-2** Should a 55-year old man who is otherwise well, with a systolic BP of 110, total cholesterol of 250, and no family history of CHD be treated with statins? (Primary prevention) Two groups of authorities debate. One says “yes”. One says “no”

***Statin Therapy Is A Critical Adjunct For Those Identified At Increased Risk Of CHD.***

***Adverse Effects Are Rare***

**YES—STATIN THERAPY FOR HEALTHY MEN IDENTIFIED AT “INCREASED RISK”**

Benefits (efficacy): Two large primary-prevention trials (WOSCOP and AFCAPS/TexCAP) included over 13 000 asymptomatic participants without a history of CHD, but with an elevated cholesterol—treated with statins vs placebo. The treated groups experienced a reduction in myocardial infarction, CHD-related deaths, and major coronary events by 31% to 40%.

Guidelines around the world support a combined lifestyle (always lifestyle changes) and pharmacologic approaches to cholesterol-lowering directed at patients with elevated CHD risk.

Harms (adverse effects): Are statins safe? Adverse effects are rare. About 5% of patients will develop muscle-related complaints. They are generally reversible after discontinuation. There is no good peer-reviewed evidence that statins lead to cognitive impairment or memory loss. The risk of development of diabetes associated with statins is mainly seen in those with preexisting glucose intolerance. Risk of diabetes is minimal in comparison with CHD event reduction.

Compliance: Do statins lead to lower adherence with a prudent lifestyle? There is evidence to the contrary. A physician's recommendation for statin therapy may motivate improvements in overall health behaviors.

Conclusion: Physicians must encourage lifestyle interventions along with medications. The cornerstone of therapy for patients with elevated cholesterol will always be dietary modifications and emphasis on physical activity. Statin therapy is a critical adjunct for those identified at increased risk of CHD.

***Statins Are Not Effective In Improving Length Or Quality Of Life When Used For Primary Prevention.***

**No—HEALTHY MEN SHOULD NOT TAKE STATINS**

Benefits (efficacy): A meta-analysis of 11 trials (65 229 healthy men and women with high cholesterol ) with over 240 000 person-years of follow-up showed no reduction in mortality associated with statin treatment. A 2011 Cochrane review of statins among persons without documented CHD came to similar conclusions. A population-based cohort studying in the UK of more than 2 million statin users reported increased risk of liver dysfunction, acute renal failure, myopathy, and cataracts. Increased risk of diabetes has been seen in randomized clinical trials. Based on the current evidence, a healthy man with elevated cholesterol will not live any longer if he takes a statin.

Harms (adverse effects): Data from observational studies show much higher rates for statin-related myopathy than the 1% to 5% reported in clinical trials. The trials had excluded up to 30% of patients with many common co-morbidities, including those with muscle pain as well as those with renal and hepatic insufficiency. Many trials also excluded those who had adverse effects of treatment during an open-label run in period. The results of randomized trials of statins likely underestimate common symptoms such as myalgia, fatigue, and other minor muscle complaints because they often collect only data on more quantifiable adverse effects such as rhabdomyolysis. Numerous anecdotal reports and small studies have suggested cognitive impairment, which would not have been captured in randomized trials. The true extent of cognitive impairment associated with statins remains understudied.

Compliance: Prescribing a statin may undermine compliance with lifestyle changes by giving a sense of false security—ie, by taking a statin, patients may eat whatever they want and not exercise.

Conclusion: Good data indicate that statins are not effective in improving length or quality of life when used for primary prevention.

JAMA April 11,2012; 307: 1491-92 “Viewpoint” first author Rita F Redberg, University of California, San Francisco

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*I enjoyed this debate. National authorities, reviewing the same data, came to different conclusions. Both sides “cherry picked” data supporting their conclusions. (Sort of like quoting scripture.) How is the lonely primary care clinician to respond? What should the public believe?*

*I would give the debate prize to the “No” side. The side in favor of statin treatment weakened their argument by introducing another risk marker—the coronary artery calcium score—an expensive, invasive, and inconvenient application in primary care. This led to a change in the basic question, which was to consider a patient with only one risk factor (elevated total-cholesterol). They also quoted results in favor of statin therapy in large trials comprising over 12 000 subjects from the population. Certainly, many, if not most, of the subjects of these trials had more than one risk factor. And would be at greater risk than the subject in the scenario.*

*The debaters disagree on the adverse effects of statins. When a foreign substance is introduced into the body, some adverse effects are inevitable. The question for statins is how many and how severe. I believe harms of statins are underreported. Any drug taken by millions of patients must be associated with uncommon adverse effects, which evade notice in randomized trials. If a statin is prescribed, the patient should be carefully followed for any possible change in feelings. Statins may be the cause. If the drug is considered essential, a N of 1 trial may help.*

*In primary care practice, most patients considered for primary prevention will have more than one risk factor. All risk factors must be treated, including dyslipidemia. However, what reason to prescribe statin for a patient who continues to smoke?*

*I believe most patients would opt for statins. “Cholesterol” is a national obsession. “Know your cholesterol” is an imperative.*

*Note the important conclusion of both sides—lifestyle is the cornerstone of therapy for dyslipidemia. If a statin is prescribed, use a low-cost generic.*

*How should the primary care clinician respond to this dilemma?—by shared decision making. Describe the pros and cons of statin therapy and ask the patient to express his personal preference.*

*Secondary prevention is another matter.*

## **VITAMIN D**

**”Costly, Confusing, and Without Credibility”**

## 1-5 INCREASING REQUESTS FOR VITAMIN D MEASUREMENTS

“Sunbathing boosts men’s sex drives” proclaimed a newspaper report. The headline was extrapolated from a cross-sectional study showing that serum 25-hydroxy-vitamin D (**25-OH-D**) concentrations—a biochemical marker of vitamin D status—correlated with circulating testosterone concentrations in men referred for angiography. But neither sun exposure nor sex drive was directly assessed.

This anecdote epitomizes what has become a bandwagon of vitamin-D-related epidemiological research, fueling headlines in the lay media.

Vitamin D has been cast in the role of a putative miracle drug, which can prevent and treat a burgeoning list of chronic diseases.

There has been a massive rise in demand for measurement of blood concentrations of 25-OH-D by the public and by physicians in the US as well as in other countries. Companies have developed new methods for determining 25-OH-D levels and have widely promoted their use. The economic burden is substantial.

Is the cost of 25-OH-D blood testing justified?

The prevalence of 25-OH-D inadequacy is high in the UK. Up to 50-% of 45-year olds were reported to be D deficient during winter months. The greatest inadequacy was in Scotland.

How should primary care physicians interpret such results? The key question is: Does knowing the serum level improve clinical practice and patient well-being? Would supplementation improve health? This is not established.

Most evidence promoting a role for vitamin D in chronic disease has been extrapolated from epidemiological studies. But these results are often limited by factors such as potential reverse causality and residual confounding. Any conclusions about causality extrapolated from observational data are premature.

Potential limitations in making causal inferences from observational epidemiological studies:

- 1) Confounding: Many risk factors are related to both 25-OH-D levels and poor health outcomes. Statistical models might be incomplete if such factors are not measured or are measured improperly. Example: Little outdoor activity (and little exposure to sunlight); obesity; low socioeconomic status; winter.
- 2) Reverse causality: If illness or pain, other factors limit exposure to sunlight this is the cause of low serum 25-OH-D rather than the reverse. Example: Many illnesses limit exposure to sunlight. Inflammation can drive down 25-OH-D levels.

3) Publication bias: Null or negative findings are less likely to be published, especially when there is overwhelming perception of a positive association.

The effectiveness of D supplements (with concomitant calcium supplements) in rickets and osteomalacia has been proven. Supplementation might reduce the risk of fracture in elderly people with osteoporosis.

However, the need to measure circulation 25-OH-D on the basis of osteoporosis determined by dual X-ray energy imaging scans is questionable because treatment is likely to include vitamin D supplements regardless of the results.

Convincing evidence that supplements reduce the risk of CVD and diabetes does not exist. Until this question is answered, we must remain cautious about the recommendations of widespread supplementation for chronic disease prevention.

Widespread testing of asymptomatic patient's 25-OH-D status is not helpful. Economic considerations are a corner stone for healthcare providers worldwide. Until randomized, controlled trials are available, stop and think critically before measuring serum 2-OH-D status, particularly in conditions not linked to bone disease.

Lancet, January 14, 2012; 379: 95-96 "Comment" first author Naveed Sattar, University of Glasgow, Scotland.

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*The history of vitamin D as related to multiple chronic diseases parallels that of many other interventions. Some observational studies reporting benefits appear, followed by more encouraging reports, and the ball keeps on rolling. Eventually, it becomes evident there is doubt. We simply do not know if the association is causal. There may be reports of harm. Enthusiasm wanes. The cycle may take decades.*

*Vitamin D deficiency is widespread. Some segments of society are especially vulnerable. (Elderly, the chronically ill, nursing home patients). Instead of measuring serum levels, I believe empiric supplementation is warranted. The benefit / harm-cost ratio is high. This approach concurs with the ethical imperative requiring us to be good stewards of medical resources. For years, we have been empirically treated millions of people with milk fortified with vitamin D.*

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