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PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 USA
To request monthly issues go to Rjames6556@aol.com

This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

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

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HIGHLIGHTS AND *EDITORIAL COMMENTS* AUGUST 2009

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

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

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

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

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

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

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

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

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

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

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

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

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

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

This is another study emphasizing the importance of life-styles in maintaining health. A primary responsibility of primary care is to encourage patients to adopt healthy lifestyles. If the general public maintained a favorable weight, ate a healthy diet, maintained physical fitness, and quit smoking, the benefit on the nation's health would be tremendous, and concern about costs of national health care would vanish.

Now—How to do it?

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

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

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

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

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

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

Spirometry in primary care: "The spirometer is to COPD what the sphygmomanometer is to hypertension." Primary care is an essential focal point for any antismoking intervention. All guidelines (except NICE) require post-bronchodilator spirometry values. However, FEV1 and other respiratory indices obtained without bronchodilation are good markers.

Handheld spirometers have been developed and improved, with user-friendliness that makes them acceptable for use in general practice. Difficulties with validation remain. A relaxation of the stringent

ATS/ERS spirometry criteria might make spirometry more accessible to primary care for case exclusion at the point of consultation and boost the rate of detection.

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

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

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

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

"A Single Dose Of Corticosteroids May Be Sufficient."

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

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

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

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

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

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

needed to treat = 3.

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

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

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

All effects were in addition to antibiotic therapy.

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

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

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

Independently Associated With Reduced Risk Of AD.

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

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

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

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

A summary physical activity score was categorized into tertiles.

a. None: 0 hours.

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

or a combination thereof.

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

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

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

Individuals were then classified into 4 groups:

Low PA + low diet score

Low PA + high diet score

High PA + low diet score

High PA + high diet score.

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

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

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

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

Hazard ratios for AD incidence by PA and diet scores:

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

(Adjusted for multiple possible confounders)

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

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

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

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

Decreased The Likelihood Of Left Ventricular Hypertrophy

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

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

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

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

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

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

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

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

"Setting a systolic target of less than 130 mm Hg instead of the usual 140 mm Hg in patients

with treatment-resistant systolic hypertension was feasible and well tolerated."

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

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

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

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

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

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

8-6 DIAGNOSIS OF VENOUS THROMBOEMBOLISM

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

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

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

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

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

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

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

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

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

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

8-7 CLINICAL APPLICATION OF SENSITIVE TROPONIN ASSAYS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

A sievert (symbol Sv; in honor of Rolf Sievert, a Swedish medical physicist) is also a SI unit. It attempts to reflect the biological effects of radiation (as opposed to the physical). It has the same dimensions as the gray—joules per kilogram. The equivalent dose to a tissue is found by multiplying the absorbed dose (in gray) by a quality factor dependent on radiation type, part of the body irradiated, the time and volume over which the dose is spread, and even the species of the subject.

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

ABSTRACTS AUGUST 2009

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

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

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

An impressive body of research has implicated modifiable lifestyle factors such as smoking, physical activity, diet, and body weight as causes of these diseases.

This study examined the extent to which 4 major lifestyle factors are associated with reduced risk of developing 4 leading causes of morbidity and mortality: diabetes, coronary heart disease (**CHD**), stroke, and cancer.

STUDY

1. Entered a prospective cohort of men age 40-65 (n = > 9 000) and women age 35-65 (n = > 14 000) between 1994 and 1998. Mean age = 48.
2. At baseline, included questions about prevalent disease, sociodemographic and lifestyle characteristics, and food frequency.
3. Followed every 2-3 years to identify incident cases of CHD, stroke, diabetes, and cancer.
4. Follow-up for a mean of 8 years. Endpoints = type 2 diabetes, myocardial infarction, stroke, and cancer.
5. Investigated 4 lifestyle factors dichotomized into 2 categories: smoking vs no-smoking; BMI < 30 vs BMI > 30; physical activity > 3.5 hours/wk vs < 3.5 hours/wk; healthy diet vs no healthy diet. Healthy diet **=** Value > median of the sum: fruits, vegetables, whole grain, and low intake of red meat. (Eating red meat below the median yielded a higher score.)

RESULTS

1. At baseline, of over 23 000 participants, 4% had 0 healthy lifestyle factors; 24% had only 1; 25% had 2; 28% 3; and 9% 4. Never smoked 48%; BMI < 30 85%; physical activity > 3.5 32%; healthy diet 50%
2. Overall, 2006 participants (9%) were clinically diagnosed as having 1 of the 4 study outcomes. 1868 had 1 event; 134 had 2 events; 4 had 3.

3. Outcomes:

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

(Although the percentage of participants with zero healthy factors was limited, a substantial number of adverse events occurred in this category, thus providing a solid baseline rate.)

5. Reductions in risks were similar in men and women.
6. Each healthy lifestyle was associated with a reduction in risk of any chronic disease. BMI under 30 exerted the largest reduction in risk, followed by never smoking, physical activity, and adherence to a healthy diet. A BMI under 30 was a particularly strong factor in reducing risk of diabetes.
7. The biggest impact of the 4 healthy lifestyles was on diabetes. Compared with participants who had no healthy lifestyles, those with all 4 had reductions of 93% for diabetes, 81% for MI, 50% for stroke, and 36% for cancer.

DISCUSSION

1. “The message from our analysis . . . is clear; adopting a few healthy behaviors can have a major impact on the risk of morbidity. The participants with all 4 healthy lifestyle factors had a reduced risk of major chronic diseases of almost 80% compared with those with none.”
2. Although improvements in some behaviors have occurred, notably the decline in prevalence of smoking, substantial proportions of the population still engage in behaviors that are not conducive to achieving and maintaining health. In this German cohort, only 9% of participants met criteria for all healthy factors. In the US population, as well, only a small fraction meets recommendations for multiple beneficial lifestyle behaviors.
3. Opportunities to improve many lifestyle behaviors of people abound. The potential for preventing morbidity and mortality from CVD, diabetes, and cancer through healthy living is enormous.
4. Each of the 4 factors was associated with a reduction in risk. Each factor contributed to risk reduction, independently of the other factors.
5. The investigators elected not to include moderate use of alcohol as a beneficial lifestyle because of the well-documented harms of alcohol abuse.
6. These data show the unfulfilled potential of preventing chronic diseases. For those with zero

favorable factors, adoption of even one promises to increase the time free of the 4 chronic diseases.

Further gains accrue and the number of such factors increase.

7. Emphasizing healthy lifestyles early in life is urgent and important

CONCLUSION

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

Archives Internal Medicine August 10/24 2009; 169: 1355-62 European Prospective Investigation into Cancer, and Nutrition-Potsdam (EPIC-Potsdam) Original investigation , first author Earl S Ford, Center for Disease Control and Prevention, Atlanta, Georgia.

An accompanying editorial in this issue of Archives (pp 1362-63) by David L Katz, Yale University School of Medicine comments and expands on this article. Before 1993, when asked what is the leading cause of death in the US, there would be only one reasonable answer—heart disease. The answers for the 2nd, 3rd, and 4th leading causes were similarly circumscribed. In that year, McGinnis and Foege1 refashioned our understanding and forever changed these answers. As of 1993, the leading cause of death in the US became tobacco use. They looked beyond the diseases that are the proximal causes of death to the causes of those diseases, the root causes of death. Half of the annual mortality toll in the country was premature.

These deaths could be deferred with the modification of 10 behaviors subject to our will: tobacco use, dietary pattern, lack of physical activity, alcohol consumption, exposure to microbial agents, exposure to toxic agents, use of firearms, sexual behavior, motor vehicle crashes, and illicit use of drugs. The list was dominated by the first 3.

In 2004, Mokdad and colleagues refreshed the perspective. Despite a decade of awareness, the same 10 modifiable behaviors, dominated by the same 3, persisted as the leading causes of both premature death and chronic disease. “And if we are once again to be updated in 2013, there is little cause to think, based on our progress to date, that we will have fared much better across an informed expanse of 2 decades, although progress in tobacco control warrants honorable mention.”

Many large studies have associated healthful living with longevity, reduced risk of various chronic diseases, and less risk of premature mortality.

The studies fundamentally reaffirm what we already know. But one true limitation is that they teach us nothing about how to get those not already choosing health on their own to join those who are.

Actual causes of death in the United States JAMA 1993; 270: 2207

Actual causes of death in the United States: 2000 JAMA 2004; 291: 1238

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

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

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

Prevalence:

COPD is a leading cause of death. The burden is expected to rise as smoking increases in developing countries. It is consistently under-diagnosed and misdiagnosed. Overall, the prevalence of COPD in the general population is an estimated 8-10% of individuals over age 40.

Prevention:

Potentially COPD can be prevented at 3 levels: 1) Primary prevention by reduction or modification of cigarette smoking—or other known risk factors. (eg, burning biomass in the home) 2) Secondary prevention by early detection by screening, generally by spirometry, and targeting individual symptoms 3) Tertiary prevention by management of identified individuals with COPD to augment health status, reduce progression and diminish exacerbations.

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

Screening and Diagnosis:

Early disease may be truly asymptomatic. Diagnosis must be confirmed by spirometry. Many individuals remain undiagnosed until their disease progresses to severe stages.

Spirometry is an important method for accurate diagnosis and effective management of COPD and asthma. It is simple, reliable, safe, and non-invasive.

The Global initiative for chronic Obstructive Lung Disease (GOLD[1]), with the agreement of the American Thoracic Society, presented a small, important step forward for spirometry thresholds for diagnosis of COPD:

> A ratio of forced expiratory volume in 1 second (**FEV1**) to forced vital capacity (**FVC**) of less than 0.7 [FEV1/FVC < 0.7], after administration of a bronchodilator, is the spirometric criterion to define COPD. No symptoms are needed. The ratio does decrease with age, leading to false positive tests. Other guidelines are available. They are similar.
>
> Staging of COPD by % of predicted FEV1 when FEV1/FVC ratio is under 0.7
>
> Mild > 80

Moderate	50-79
Severe	30-49
Very severe	<30

Early diagnosis can be compared with screening programs for hypertension and hyperlipidemia.

The American College of Physicians and the USPSTF recommends that screening spirometry should *not* be preformed on asymptomatic persons.

Although not proven, intervention at a very early stage might reduce the likelihood of developing future COPD.

Identification of patients with symptomatic COPD remains an important challenge. Many individuals will go to see their family M.D. with symptoms, but either the diagnosis of COPD is not considered, or they will be labeled as having smoker's cough, or diagnosed as lower respiratory infection or asthma. Individuals who do not consult a doctor might be in denial or have negative impression of the values of seeking medical care. Historically, nihilism surrounds COPD. Patients deny the problem exists.

. "The spirometer is to COPD what the sphygmomanometer is to hypertension."

Spirometry in primary care:

Spirometry might find large numbers of asymptomatic patients who have COPD. Some researchers concluded that by testing one smoker a day, on average, primary care practitioners could identify one patient with COPD each week.

Primary care is an essential focal point for any antismoking intervention. Efforts to establish primary-care centers as hubs for spirometry have achieved mixed results. Good quality spirometry should be used extensively in primary care as well as in specialty medicine. Use will reduce the burden of COPD and have a real effect on public health.

Pre-bronchodilator vs post-bronchodilator spirometry:

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

Guidelines for bronchodilation differ as to how and when and what inhaled drug to use. .

If the bronchodilation method is not standardized, why do guidelines call for it?

Local spirometry reference values for the U.S. population have been reported by NHANES II in 1999 and are used widely according to age, sex, height, and ethnic origin, [2]

Spirometry results need clinical interpretation, with a minimum time commitment of 2-10 minutes. The best laboratories disregard at least 20% of patients-data because of technical inadequacies. Failed spirometry is more common in the elderly, high GOLD stage, female sex, and poor education.

Apart from clinical trials or specialist settings, inclusion of tests of suboptimal quality might reduce our degree of uncertainty for clinical decision-making. “Surely, if a patient attempts the spirometry test, but is unsuccessful, some information is better than no information at all for a diagnosis to be made.”

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

Treatment:

We must treat tobacco addiction as a chronic relapsing disorder.

Simple brief advice for health professionals increases the chance of cessation.

In smokers, the slope of loss of lung function can be attenuated by cessation of smoking. One study prospectively examined the effect of smoking-related disease on loss of respiratory reserve. Those who stopped smoking at age 45 changed the slope of FEV1 decline to that recorded in healthy non-smokers. Stopping smoking at age 65 in persons whose FEV1 at that time was reduced to 30% of predicted, enhanced survival compared with those who continued to smoke. (It’s not too late to stop.)

A number of large studies report that cessation of smoking results in a small improvement in lung function at one year, and reduced rates of decline thereafter. In addition, those who quit had a lower risk of death from lung cancer and coronary artery disease.

Swift and sustained reductions in cough, phlegm, and wheeze were recorded in smokers who were able to quit.

Smoking cessation is the only intervention that convincingly slows progress of the disease, although cessation in persons with COPD is more difficult than in healthy smokers. The disease will certainly progress if smoking continues.

Prognosis:

Undetected disease could go on to cause substantial morbidity and mortality.

In any assessment of individuals, respiratory symptoms such as chronic cough, phlegm, and shortness of breath while walking, are of major importance for predication of long-term clinical outcomes in patients with COPD with mild obstruction.

The prospective Lung Health Study followed 6000 subjects with mild-moderate COPD (mean 78% of predicted FEV1). Subjects were offered a smoking-cessation program. About 25% stopped smoking completely and another 25% stopped to the end of the study. Those who stopped smoking showed a small improvement in lung function over the first year, and had reduced rates of decline thereafter. At an

11-year follow-up, almost all smokers who were abstinent at 5 years remained abstinent. Those who continued to smoke lost, on average, 30 mL of expiratory volume per year more than quitters.

Some factors associated with COPD development might not be preventable: Aging; repeated respiratory infections; co morbid asthma; and genetically acquired antitrypsin deficiency.

Lancet August 29, 2009; 374:721-32 doi:10.4104/pcrj.2009.00055 Review article, first author Joan B Soriano, Center for Advanced Respiratory Medicine, Barcelona, Spain

1 www.goldcopd.com

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

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"A Single Dose Of Corticosteroids May Be Sufficient."

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

Treatment of sore throat with antibiotics provides only modest benefit in reducing symptoms and fever. Prescribing rates remain disproportionately high, leading to antibiotic resistance and medicalization.

The pressure for clinicians to reduce antibiotic use for sore throat leaves a therapeutic vacuum.

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

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

STUDY

1. Literature search included 8 randomized controlled trials of 743 patients (half children; half adults) comparing systemic corticosteroids with placebo in outpatient settings. All had clinical signs of acute tonsillitis, pharyngitis, or a clinical syndrome of "sore throat".
2. About half had exudative sore throat; half had group A beta-hemolytic streptococcus infections.
3. All received antibiotics and analgesics.
4. Randomized to corticosteroids vs placebo.

RESULTS

1. In a pooled analysis of 4 trials, patients treated with corticosteroids were three times more likely to

have complete remission of pain at 24 hours, Number needed to treat to benefit one patient = 4. Significant results were recorded in adult patients only, and in those receiving oral corticosteroids.

2. In 3 trials, corticosteroids increased likelihood of complete resolution of pain at 48 hours. Number needed to treat = 3.
3. In patients with exudative sore throat, corticosteroids reduced the mean time to onset of pain relief (mean difference = 6 hours). All 3 categories of sore throat (exudative, bacterial, and severe) had reduced time to onset of pain relief.
5. Time to onset of pain relief was similar in trials of adults only. No significant changes in children.
6. Time to onset of pain relief was similar when oral and intramuscular corticosteroids were used.
7. Time to complete resolution of pain in 5 trials ranged from 15 to 45 hours in the corticosteroids groups vs 35 to 54 hours in the placebo groups.
8. Three studies reported no difference in days missed from school or work.
9. One trial reported increased recurrence rate in the placebo group.

DISCUSSION

1. Corticosteroids significantly increased the proportion of patients with sore throat who experience complete relief of pain at both 24 and 48 hours.
2. Fewer than 4 patients needed to be treated with corticosteroids to prevent one patient from continuing to experience pain at 24 hours.
3. All effects were in addition to antibiotic therapy.
4, “The effects of corticosteroids on resolution of pain were most apparent in the initial 24 hours, which implies that a single does of corticosteroids may be sufficient.”
5. Effects of corticosteroids alone (without antibiotics) are not known.
6. Benefits on children were not clear due to limitations of reporting in trials which included children.

CONCLUSION

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

BMJ August 29, 2009; 339: 488-90 [BMJ2009;339:b2976] Original investigation, first author Gail Hayward, University of Oxford, UK

Independently Associated With Reduced Risk Of AD

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

Physical activity (**PA**) can slow down functional decline associated with aging and improve health in older individuals. Regarding Alzheimer disease (**AD**),the relationship is less clear. Studies report conflicting results.

A previous study by these authors reported that higher adherence to the Mediterranean diet (**MD**) is associated with a lower risk of AD and mild cognitive impairment.

The effect of combined MD + PA on AD has not been studied. This study examined the effect of the association.

STUDY

A. Neuropsychological status

1. Included two cohorts (n = 1880; mean age 77) recruited through a neighborhood aging project 1992-99. None had dementia at baseline.
2. At entry, recorded each individual's medical and neurological history. A structured interview assessed health and function. A neuropsychological battery tested memory, orientation, abstract reasoning, language, comprehension, and visual-spatial abilities.
3. Grouped data on 15 neuropsychological tests into 4 cognitive factors: memory, language, processing speed, and visual-spatial ability. Averaged them to create a composite cognitive score.
4. Repeated evaluations every 1.5 years through 2006.
5. Made a consensus diagnosis for presence or absence of dementia. And type of dementia.

B. Physical activity

1. Assessed physical activity by a leisure-time questionnaire—the number of times and the number of minutes participating in 3 categories: vigorous, moderate, and light.
2. A summary physical activity score was categorized into tertiles.
    a. None: 0 hours.
    b. Some: 0.1 hours of vigorous and 0.8 hours of moderate, or 2.3 hours of moderate or light or a combination thereof.
    c. High: 1.3 hours of vigorous, 2.3 hours of moderate or 3.8 hours of light, or a combination thereof.

C. Diet

1. Obtained average food consumption information over the past year with a food intake

questionnaire.

2. Constructed a MD diet score. Assigned a value of 1 for each *beneficial* component: fruits, vegetables, legumes, cereals, fish, a ratio of monounsaturated fat to saturated fat, and mild to moderate alcohol consumption *above* the median. Also assigned a value of 1 for each *detrimental* component (meat and dairy) *below* the median.
3. The diet score was the sum (range 0 to 9 with the higher score indication higher adherence. The summary score was analyzed into tertiles: low 0 to 3; middle 4 to 5; high 6 to 9.

D. Individuals were then classified into 4 groups:

Low PA + low diet score

Low PA + high diet score

High PA + low diet score

High PA + high diet score.

RESULTS

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

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

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

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

3. Hazard ratios for AD incidence by PA and diet scores:

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

(Adjusted for multiple possible confounders)

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

DISCUSSION

1. “The study suggests that more physical activity is associated with a reduction in risk of developing AD.” The gradual reduction in risks for higher tertiles of PA suggests a possible dose-response.
2. Cardiovascular fitness has been related to lower age-related brain atrophy in magnetic resonance

imaging. Increased PA has also been associated with reduction in inflammation, increased concentration of various neurotransmitters, and increased insulin growth factor.

3. Both healthy eating and participating in PA may independently lower risk of AD.
4. Both the dietary and physical activity measures demonstrated relative stability over time, but individuals who developed dementia reported a higher decline in both PA and MD adherence.

CONCLUSION

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

JAMA August 12, 2009; 302: 627-37 Original investigation, first author Nikolaos Scarmeas, Columbia University Medical Center, New York.

A companion study in this issue of JAMA (pp 638-48) "Adherence to a Mediterranean Diet, Cognitive Decline, and Risk of Dementia", first author Catherine Feart, INSERM, University Victor Segalen, Bordeaux, France, reports that over 5 years, a MD was associated with slower MMSE cognitive decline, but was not consistently associated with any other cognitive tests. Higher adherence was not associated with incident dementia.

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Decreased The Likelihood Of Left Ventricular Hypertrophy

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

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

Present evidence supports reduced thresholds of diastolic BP in patients with type-2 diabetes.

The 2007 guidelines of the European Society of Hypertension emphasized that the value to which systolic BP should be lowered in patients is unknown.

This study tested the hypothesis that tight control (systolic < 130) vs usual control (systolic < 140) of systolic BP would be beneficial in non-diabetic patients with hypertension.

STUDY

1. This multicenter, open-label randomized trial in Italy entered 1111 non-diabetic patients with

hypertension. (Present guidelines already recommend tight BP control in diabetics.) All were over age 55 and had a systolic BP of 150 or higher. (Mean BP = 163/90)

2. Patients had at least one additional risk factor (cigarette smoking, total cholesterol > 200 mg/dL LDL-cholesterol > 120, HDL-cholesterol < 40, family history of premature cardiovascular disease in a first-degree relative, previous TIA or stroke, established CVD or peripheral vascular disease).
3. Randomly assigned to a target systolic of 1) less than 140 [usual control], or 2) less than 130 [tight control]
4. Used open-label agents to reach targets. (Various combinations of a diuretic, ACE inhibitor, angiotensin blocker, calcium blocker, and beta-blocker. (Furosemide, ramipril, telmisartan, amlodipine, bisoprolol.) Choice of drug was left up to the individual investigator. In the tight control group, any BP reading over 130 at any visit led to intensification of treatment. In the usual-control group, any BP < 130 led to down-titration of treatment.
5. Primary end-point = left ventricular hypertrophy determined by ECG at 2 years. (LVH is an intermediate outcome that is a strong predictor of cardiovascular outcomes.)
   Secondary outcome = composite of all-cause mortality, fatal or non-fatal stoke , TIA, congestive heart failure, new-onset atrial fibrillation, angina pectoris, aortic dissection, occlusive peripheral vascular disease, and renal failure.
6. Checked BP every 4 months with 3 consecutive readings on a standard mercury sphygmomanometer after the patients had been seated for 10 minutes. BP was the average of the 3 readings. Checked ECG at baseline and every year.
7. Analysis by intention-to-treat. Median duration of follow-up = 2 years.

RESULTS

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

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

5. Occurrence of coronary revascularization and new atrial fibrillation was lower in the tight control group.
6. Adverse reactions were generally mild and did not vary between groups. Low serum potassium occurred in 3 patients.
7. Subjects in the tight control group were more likely to receive diuretics and angiotensin-receptor blockers. No difference in use of other drugs.

DISCUSSION

1. "Setting a systolic target of less than 130 mm Hg instead of the usual 140 mm Hg in patients with treatment-resistant systolic hypertension was feasible and well tolerated."
2. Over 2 years, tight, compared with usual control in non-diabetic patients with uncontrolled BP at baseline, resulted in a reduction in systolic BP. This resulted in decreased likelihood of left ventricular hypertrophy and the incidence of a composite cardiovascular outcome.
3. Although LVH is usually described as an intermediate endpoint, LVH determined by ECG is a powerful and independent predictor of outcome.
4. In the Framingham Heart Study, patients with LVH at baseline and a serial increase over time in the ECG voltages were twice as likely to have a cardiovascular event during the subsequent 2 years than those with a decrease in voltage.

CONCLUSION

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

Lancet August 15, 2009; 374: 525-33 Original investigation, first author Paolo Verdecchia, Hospital S Maria della Miseracordia, Perugia, Italy Cardio-Sis Study

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"D-Dimer Tests Can Help Management But Cannot Replace Clinical Judgment"

8-6 DIAGNOSIS OF VENOUS THROMBOEMBOLISM

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

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

Now, second generation assays provide results within an hour. Point-of-care tests produce results within 10-15 minutes.

An article in this issue of BMJ[1] analyzed the diagnostic performance of several qualitative and quantitative tests used at the point-of-care. Quantitative tests perform better than qualitative ones. Their results confirm the value of a negative test in excluding the diagnosis of VTE . But some tests are still imprecise. Quantitative tests used at the point-of-care have been poorly evaluated in patients with suspected PE.

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

The authors used Bayes' theorem to calculate the post-test probability of VTE as a function of pretest probability. They assumed a pre-test threshold probability of 2%, below which further testing was not warranted.

Point–of-care D-dimer tests are particularly useful for doctors who need rapid information. Negative results may eliminate the need for further diagnostic testing in almost 30% of patients with suspected VTE. In day-to-day practice, such easy tests carry some risks. They are sometimes ordered in patients with an obvious explanation for their signs and symptoms.

In the best case scenario, the test will be negative with the loss of little time and money. In the worst case scenario, a positive test will prompt further testing such as ultrasonography or CT, which carries risks of iatrogenic events and false positive results.

One of the most common reasons for inappropriate testing is the lack of evaluation of clinical probability. We have to follow some evidenced-based rules:

Use tests with confirmed diagnostic performance.

Consider different diagnoses and their clinical probabilities before performing any test.

Perform tests that will lead to a post-test probability low enough to rule out the disease if the test is negative, and high enough to diagnose the disease if the test is positive.

A key point is how doctors apply Bayesian reasoning in day-to-day clinical practice.

An article in NEJM 2003[2] gives help in deciding the pretest probability of deep venous thrombosis.

The Pulmonary Embolism Rule-out Criteria[3] can help decide who to test. (Ie. to help estimate pretest probability.)

BMJ August 22, 2009; 339: 412-13 Editorial by Pierre-Marie Roy, Centre Hospitalieir Universtaire, Angers, France.

1 Excluding Venous Thromboembolism using point-of-care D-dimer tests in outpatients BMJ August 22, 2009; 339: 450 First author G J Geersing, University Medical Centre Utrecht, Utrecht, Netherlands (BMJ 2009;339:b2990 for full text)

What is the diagnostic accuracy of currently available point-of-care D-dimer tests in particular for excluding VTE in suspected outpatients?

Point-of-care tests can safely exclude VTE in low risk patients.

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

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

Pretest likelihood of VTE	Post test probability of VTE given a negative test result
Low risk (5%)	0.4 (Ie, very unlikely to be VTE)
Moderate risk (20%)	1.7
High risk (50%)	6.5

2 Wells et al NEJM 2003;349:1227-35

Consider factors to judge pretest probability of deep vein thrombosis (**DVT**)

Active cancer

Immobilization of lower extremity

Recently bedridden > 3 days or surgery within 12 weeks.

Localized tenderness along distribution of deep venous system

Entire leg swollen

Calf swollen 3 cm or more than asymptomatic leg (measured 10 cm below tibial tuberosity

Pitting edema confined to symptomatic leg

Collateral superficial veins (non-varicose)

Previous DVT

(If both legs affected, use more symptomatic leg)

All given 1 point

Alternate diagnosis at least as likely as DVT subtract 2 points

Score 2 or higher indicates likelihood of DVT; 0 or 1 point DVT, unlikely

3 Righini et al Lancet 2009 ;371:1227-35 Diagnosis of pulmonary embolism by multidetector CT alone, or combined with venous ultrasonography of the leg.

Consider 6 factors which may lessen probability of PE

Age < 50

Pulse < 100

No unilateral leg swelling

No hemoptysis

No recent surgery

No prior DVT

No hormone use

If all 6 negative, there is less than a 1.8% probability of PE. This is below the point where it is not worth it for patients or society to pursue further diagnosis or treatment.

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

8-7 CLINICAL APPLICATION OF SENSITIVE TROPONIN ASSAYS

Since 1999, professional societies have recommended use of troponin as the preferred biomarker for evaluation of patients with suspected myocardial infarction (**MI).** Troponins replaced creatine kinase-MB.

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

Two articles in this issue of NEJM[1,2] reveal the advantages and limitations of STA.

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

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

Nevertheless, on the basis of the outdated guidelines, many laboratories continue to report an "inconclusive" or "suggestive" range using the 2 cutoff values.

The progressive enhancement of the analytic performance of troponin assays has reduced the incidence of false positives (an elevated value in the absence of MI). As a result of better precision, the new assays are more sensitive (more positive tests when MI is present), and can detect substantially lower concentrations of troponin. This has led to two critical questions:

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

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

The two studies report highly consistent results. For diagnostic performance, the accuracy for the diagnosis of MI was improved with the sensitive assays (94 to 96%) as compared with the older assays (85 to 90%). In study 1, the improved accuracy of the new assay for MI was most pronounced soon after the onset of chest pain. And the clinical sensitivity at the 99th percentile cutoff value increased from 64% to 91%. In study 2, the accuracy of the sensitive assays within 3 hours after onset of pain was 92 to 94%, as compared with 76% for the old standard assay.

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

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

It is essential to differentiate between the tissue specificity of troponin for cardiomyocyte injury and the clinical specificity for MI (myocytes injury due to ischemia). The adoption of troponin has revealed the occurrence of myocardial injury in many conditions in which it was not previously detected with use of CK-MB. This has given the impression of an increased number of false positive results (for MI). However, this does not impugn the tissue specificity of troponin, rather it underscores that myocardial injury may result from a variety of mechanisms. It also shows that a clinical diagnosis of MI depends both on elevated levels of troponin and on clinical data (ie, the presence of typical symptoms that support ischemia as the cause). It is not possible to reliably discriminate ischemia from non-ischemic cause (eg, myocarditis) by simply raising the cutoff value. A rising or falling pattern of troponin values is helpful in discriminating acute injury from chronic causes (eg, end-stage kidney disease). Imaging techniques (eg MRI) are likely to play an increasing role in distinguishing patterns of myocardial injury.

The prognostic implications of low-level increases in troponin that are detected by sensitive assays:

At least 6 studies have firmly established the prognostic relevance of small elevations of STA. Collectively these data indicate a doubling of the adjusted risk of death or recurrent ischemia in patients with a small troponin elevation.

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

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

NEJM August 27, 2009; 361: 913-15 Editorial by David A Morrow, Brigham and Women's Hospital, Boston Mass.

1 "Early Diagnosis of Myocardial Infarction with Sensitive Cardiac Troponin Assays" NEJM August 27, 2009; 361: 858-67 first author Tobias Reichlin, University Hospital Basel, Switzerland

"The diagnostic performance of sensitive cardiac troponin assays is excellent." They can substantially improve the early diagnosis of acute MI, particularly in patients with a recent onset of chest pain. (Including those presenting within 3 hours.)

There are 4 STAs available: Abbott-Architect Troponin I; Roche High-Sensitive Troponin T ; Roche Troponin I; and Siemens Troponin I Ultra. The old standard assay was Roche Troponin T.

2. "Sensitive Troponin I Assay in Early Diagnosis of Acute Myocardial Infarction" NEJM 2009; 361: 868-77 First author Till Keller, Johannes Gutenberg University, Mainz, Germany

The use of a sensitive assay for troponin I (Troponin I Ultra-Siemens) improves early diagnosis of acute myocardial infarction and risk stratification, regardless of the time of chest pain onset.

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"As Many As 2% Of Cancers May Be Attributable to Radiation Exposure During CT Scanning"

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

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

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

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

This study estimated the total effective dose of radiation from medical imaging in a large adult population, excluding the elderly.

STUDY

1. Retrospective cohort study used claims data from a large health care organization (Over 26 million people (age 18-64) in 5 centers between 2005-2007.)
2. Examined all claims from hospitals, outpatient facilities, and physician's offices for codes that identified imaging procedures involving radiation. Excluded all radiation procedures given for therapeutic purposes (eg, for breast cancer).
3. Categorized procedures as plain radiography, CT, fluoroscopy (including angiography), and nuclear imaging.
4. Obtained estimates of effective radiation doses (assessed in millisieverts; mSv) from the published literature. The effective dose is a measure designed to represent the overall detrimental biological effect of a radiation exposure. It is calculated by weighing the concentrations of energy deposited in each organ from a radiation exposure with the use of parameters that reflect the type of radiation and the potential for radiation-related mutagenic changes in each organ in a reference subject. This allows for useful population-level comparisons across different types of radiation exposure.

RESULTS

1. Identified over 950 000 subjects, mean age 36. Identified a total of 3,442,111 imaging procedures associated with radiation exposure in 655,613 (69%) subjects over the 3 years—a mean of 1.2 procedures per person per year.
2. The mean effective dose was 2.4 mSv per person year. The median effective dose was 0.1 mSv per person year. (This indicates that many outliers received large radiation doses.)
3. The proportion of subjects undergoing at least one procedure was higher in the older age group (50% of those age 18-34 vs 86% of those age 60-64). More women than men underwent at least one procedure.
4. Moderate doses (3-20 mSv /y) were incurred at an annual rate of 194 per 1000 enrollees; high doses (>20-50 mSv/y) at an annual rate of 19% per 1000; and very high doses (> 50 mSv) at an annual rate of 2 per 1000.
5. Average effective dose mSv

Myocardial perfusion imaging	15
CT angiography of chest (non-coronary)	15
Percutaneous coronary intervention	15
CT of abdomen, pelvis or chest	6-8
Upper GI series	6

Nuclear bone imaging	6
CT of cervical spine	6
CT of lumbar spine	6
Intravenous urography	3
Thyroid uptake	2
Mammography	0.4
PA chest radiograph	0.02

7. Many procedures were performed on multiple occasions in the same patient.
8. Exposure is of greatest concern in younger patients (age 18-43). 50% received at least one procedure). Rates for high and very high exposure were not trivial in younger patients. More than 30% of men and 40% of women under age 50 received doses exceeding 20 mSv.
9. Related risks accrue over a lifetime. Cancer may be more likely to develop in women than in men after similar levels of exposure.
10 Most radiation exposures occurred in outpatients.

CONCLUSION

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

NEJM August 27, 2009; 361: 849-57 Original investigation, First author Reza Fazel, Emory University School of Medicine, Atlanta, GA.

An editorial in this issue of NEJM (pp 841-43) by Michael S Laurer, National Heart, Lung, and Blood Institute comments and expands on this article.

Physicians in the US are referring their patients for so many imaging tests that as many as 2% of cancers may be attributable to radiation exposure during CT scanning.

But our medical system sees nothing wrong with this. Patients are pleased to receive the best of cutting technology, especially if their insurance pays for it. Physicians can defend the practice because their specialty societies argue than the procedures are “appropriate”. Defenders of the procedures say that it is logical that imaging tests may identify patients for whom aggressive therapies should improve the outcome. But this logic represents only a hypothesis, not a proof.

The issue of radiation exposure is unlikely to come up because each procedure is considered in isolation, the risks of each procedure are low. (The danger of one procedure may be small, but procedures are cumulative. Any cancer resulting will not appear for years and cannot be easily linked to past imaging. Oncogenesis associated with each sublethal dose goes unrecognized because it is neither accurately measurable nor predictable for the individual.

When skeptics complain about excessive costs for unnecessary imaging procedures, it is easy to dismiss them for advocating “rationing”.

“Overall, we must conclude that with few exceptions—such as mammography—most radiologic imaging tests offer net negative results.”

“Use of ionizing radiation carries an element of danger in every procedure.”