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FOR
PRIMARY CARE

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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 5 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 2006

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

8-1 PRIMARY CARE—WILL IT SURVIVE?

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

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

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

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

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

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

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

Increased computer use may help.

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

For a different view, see the following abstract.

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

(This editorialist comments on some of the positive aspects of PC.)
"Taking care of patients as their primary care doctor is the best job in medicine."

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

Read the full abstract.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Follow-up a mean of 4.5 years.

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

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

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

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

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

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

Another Application of the Delayed Prescription

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

It seems to me that the problems are: staph are ubiquitous, the carrier rate is high, and the tendency to mutate is also high. This leads to recurrent and changing antibiotic resistance. Distinguishing hospital acquired infections from community acquired infections, I believe, is arbitrary. Our challenge is to be ever vigilant for mutations, and to keep up with the antibiotic-resistant and sensitive profile. .Meanwhile application of traditional sanitary methods of reducing likelihood of spread of the infection remains paramount.

"Potentially Pose A Nightmare Scenario"

8-7 THE TREATMENT TRIANGLE FOR STAPHYLOCOCCAL INFECTIONS

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

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

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

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

1) Drainage and debulking

2) Wound culture

3) Antibiotic therapy

The weight is on drainage and debulking.

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

Harm Outweighs Benefit

8-8 CELECOXIB FOR THE PREVENTION OF SPORADIC COLORECTAL ADENOMAS

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

Adverse events were more common in the celecoxib groups

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

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

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

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

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

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

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

A good rule—use acetaminophen first.

As Effective and As Safe As LMWH. Suitable for Outpatient Treatment.

8-9 COMPARISON OF FIXED-DOSE WEIGHT-ADJUSTED UNFRACTIONATED HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN FOR ACUTE TREATMENT OF VENOUS THROMBOSIS.

This trial was designed to determine if fixed-dose weight-adjusted unfractionated heparin given s.c is as effective and safe as LMWH in treatment of VTE.

Randomized, non-inferiority trial followed over 700 patients (mean age 60) with acute VTE. All had newly diagnosed VTE confirmed by venography or ultrasonography, or pulmonary embolism confirmed by CT angiography.

Randomized to:

1) Unfractionated heparin given s.c.—initial dose = 333 U/kg; followed by 250 U/kg every 12 hours.

2) LMWH (dalteparin or enoxaparin) given s.c at a dose of 100 IU/kg every 12 hours.

No coagulation tests were used to modify doses.

Both drugs were administered for at least 5 days. Both were overlapped with warfarin, usually started on the first day as heparin, and continued for at least 5 days. Most subjects were treated as outpatients.

Recurrent VTE	Unfractionated heparin (n = 345)	LMWH (n = 352)
Three months	13 patients (3.8%)	12 patients (3.4%)
DVT recurrence	11 patients	8 patients
PE	2 patients	4 patients.
Deaths 3 months	5.2%	6.3%
Major bleeding (1st 10 days)	4 patients (1.1%)	5 patients (1.4%)

Conclusion: Fixed-dose subcutaneous heparin is as effective and as safe as LMWH of initial treatment of venous thromboembolism. It is suitable for treatment of outpatients. It is much less expensive.

A disadvantage of unfractionated heparin is that it is more likely to cause heparin-induced thrombocytopenia (with sometimes devastating thrombotic complications) than is LMWH. However, it occurs rarely.

The benefit/harm-cost ratio of s.c. unfractionated heparin is much higher than the ratio for LMWH because the cost is so low in comparison.

Associated With Reduced Risk Of Rupture Of AAA

8-10 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND AORTIC RUPTURE

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

Retrospective, population-based, case-control study included consecutive patients older than

age 65 (n = over 15 000; the majority men; mean age = 75) admitted to hospitals in Ontario between 1992 and 2002. All had a primary diagnosis of AAA. About ¼ were ruptured; ¾ were intact.

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

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

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

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

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

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

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

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

Remember smoking is strongly associated with risk of AAA.

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

"The Reduction In The Risk Of Fatal Stroke Was Consistent With The Treatment Effect, but Not Significant."

8-11 HIGH-DOSE ATORVASTATIN AFTER STROKE OR TRANSIENT ISCHEMIC ATTACK

This randomized trial compared the effect of high dose atorvastatin (*Lipitor*) vs placebo on risk of stroke after a first episode. (Secondary prevention.)

Randomized over 4700 patients (mean age 63) to: 1) Atorvastatin 80 mg daily, or 2) Placebo.

All patients had a stroke or TIA within 6 months of entry. None had known coronary heart disease. Patients with atrial fibrillation were excluded. Median follow-up = 5years.

Stroke over 5 years (primary outcome)	Atorvastatin	Placebo
Non-fatal stroke	10.4 %	11.8 %
Fatal stroke	1.0 %	1.7 %

(NNT to prevent one non-fatal stroke in 5 years = 71; to prevent one fatal stroke = 143)

Overall mortality (number of deaths)	216	211
Number of patients with hemorrhagic stroke	55	33

(*Ie, no reduction on overall mortality; and an increase in hemorrhagic stroke.)*

Elevation of liver enzymes	2.3%	0.5%
Any adverse event resulting in discontinuation of study treatment	17.5%	14.5%

"Our results support the concept that, from the standpoint of statin treatment, stroke or TIA should be considered a coronary heart disease risk equivalent." "The potential risk of recurrent hemorrhage should be considered when one is deciding whether to administer a statin to patients who have had a hemorrhagic stroke."

Conclusion: In patients with a recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin over 5 years slightly reduced overall incidence of stroke and cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke. Mortality was not reduced.

The study was supported by Pfizer. Look for the "spin".

I would not prescribe 80 mg of atorvastatin for secondary prevention of stroke:

Benefits are not, in my opinion, clinically significant.

It is associated with considerable "bother".

Need for more frequent checks of liver enzymes.

More risks (increased hemorrhagic stroke).

More withdrawals.

Lipitor 80 mg daily for 5 years costs $7500.00. (My calculation.)

The "Money Needed to Treat" **(MNT)** *to benefit one patient over 5 years = $7500 X 72 = $540 000, and to prevent one fatal stroke = $1 072 000*

The benefit / harm-cost ratio of high dose atorvastatin to prevent one recurrent stroke over 5 years is very low.

A more clinically rewarding study of atorvastatin for secondary prevention of ischemic stroke would have compared 10 mg with 80 mg, or to compare with a less expensive, low dose of a generic statin.

Note that many patients in the study had risk factors for stroke and coronary disease at baseline: smoking, hypertension, diabetes, overweight. Lipid control is not the only treatment goal. I presume many patients were treated for these risk factors, but the emphasis was on lipid control—taking a pill vs not taking a pill. This is not the way primary care is practiced.

I believe statin therapy is indicated for primary as well as secondary prevention of ischemic (not embolic) stroke. Although the NNT to benefit one patient will be high, I believe lower doses of less expensive statins (eg, generic simvastatin) would likely be associated with prevention of a second episode, and to a lesser extent a primary episode, and be less likely to cause adverse effects and bother.

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

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

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

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

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

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

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

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

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

You May Set Off The Alarm and be Strip-searched

You Should Avoid Conceiving for A Year

8-13 TRIGGERING RADIATION ALARMS AFTER RADIOIODINE TREATMENT.

WHAT TO TELL PATIENTS ABOUT RADIOIODINE THERAPY

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

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

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

An accompanying article suggests several precautions for patients receiving radioiodine therapy

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

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

ABSTRACTS AUGUST 2006

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8-1 PRIMARY CARE—WILL IT SURVIVE?

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

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

Many primary care physicians **(PCPs)** are unhappy with their jobs. The editorialist lists a number of reasons:

1) Demands on PCPs:

A growing number of demands are being placed on PCPs. They face a seemingly insurmountable task. The number of primary care tasks has grown. PCPs are expressing frustrations that the knowledge and skills they are expected to master exceed the human capabilities, making it impossible to provide the best care for every patient.. The scope of PC extends from uncomplicated upper respiratory and urinary tract infections to the longitudinal care of elderly patients with diabetes, coronary heart disease, arthritis and depression. The prevalence of chronic conditions—most of which are handled in PC—is increasing.

The preventive services that the physician ought to provide because there is evidence of efficacy, or might provide because of the patient's preferences (which must therefore be discussed) have multiplied. It has been estimated that it would take 10 hours per working day to deliver all recommended care for patients with chronic conditions, plus 7 hours per day to provide evidence-based preventive care, to an average panel of 2500 patients. (The mean PC panel size is 2300). The reality is that PCPs lack the time to provide all evidence-based preventive and chronic care services for the average patient. (*Study time in order to "keep up" with the evidence is not included*.)

2) Communication with patients:

Communications with patients are becoming more complex and difficult. The time allotted for each consultation and communication is limited. The quality of care is uneven. Many patients are medically illiterate. Many are not proficient in English. The majority of patients with diabetes, hypertension, and other chronic diseases leave the doctor's office without having understood what the physician said. (*It takes time to listen, and then to explain, and then to determine if the patients understands.)*

3) Reimbursement:

Reimbursement is inadequate. It is based primarily on *quantity* of services rather than on *quality*. This forces PCPs onto a treadmill and devalues their professional work life. The short rushed visits with overfilled agendas that cause patient dissatisfaction simultaneously breed frustration in physicians.

The system of physician payment exacerbates the problem. The median income of PCPs is about ½ that of specialists. Inflation adjusted income of PCPs has actually fallen in the past 10 years.

Many nurse practitioners and physician assistants are joining wealthier specialty practice instead of going to work in primary care.

4) Patients views:

The great majority of patients prefer to seek initial care from a PCP rather than a specialist, but their unhappiness with their primary care is growing.

The short rushed visits with overfilled agendas that cause patient dissatisfaction.

Patients report that they cannot schedule timely appointments.

Many face communication problems. Many may have limited proficiency in English and require an interpreter. Many patients are medically illiterate. This increases the complexity and underlies the quality of the consultation.

These excessive demands contribute to long waiting times and inadequate quality of care, and causes an overflow in emergency departments.

All this is occurring at the time of growing need for primary care of the aged, and increasing prevalence of chronic disease.

Primary care based health care has the potential to reduce costs while maintaining quality. The hospitalization rates for diagnoses that could be addressed in ambulatory care settings are higher in geographic areas where access to PC is more limited. States with a higher ratio to PCPs to population have lower per-beneficiary Medicare expenditures, and higher scores of performance measures than states with more specialists per capita.

"Few legislators, particularly among those responsible for the trend setting Medicare program, are aware that primary care is struggling." "Action is needed to calm the waters before the levees break."

NEJM August 31, 2006; 355: 863-64 "Perspective", commentary by Thomas Bodenheimer, University of California, San Francisco.

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

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

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

The opportunity to develop long-term relationships with patients is only one of the many rewarding aspects of being a primary care physician.

PCPs see first hand how social factors affect patients who have chronic diseases. PCPs are often the only doctors whom the patient visits. They must identify problems that are frequently difficult to talk about (alcohol and drug use, domestic violence, risky sexual practices).

Primary care may be part of a larger social and political movement toward more equitable health care. A strong PC infrastructure is associated with better health outcomes, lower costs, and a more equitable health care system. Primary care is the key

With all the changes in our health care system, one thing remains constant: the needs of patients. Patients want a continuing relationship with a doctor whom they can trust, and they increasingly need the doctor to act as an advocate to help them get the best care within a fragmented health care system.

NEJM August 31, 2006; 355: 864-66 "Perspective", commentary by Beverly Woo, Harvard Medical School, Boston Mass

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

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

Epidemiologic evidence indicates that obesity, defined by a body mass index (**BMI**[1]) of 30 or more is associated with increased risk of death.

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

The presence of preexisting chronic disease and smoking can distort the true relation between bodyweight and risk of death. (Chronic illness and smoking are related to both a decrease in BMI and increased risk of death.)

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

Conclusion: Overweight is associated with an increased risk of death.

STUDY

1. In 1995-1996 the AARP sent out health questionnaires to members soliciting information on demographic and anthropometric characteristics, dietary intake, and numerous health-related behavioral patterns. Over 500 000 replies were received. Mean age at baseline = 62
2. Calculated the BMI using height and weight provided by the subjects.
3. Considered a subset of subjects whose weight at 50 was reported and who had never smoked. (This was an effort to assess with less bias the effect of BMI alone. The mean age of subjects in the study was 62. Determining the BMI at age 50 (an average of 12 years earlier) is one way of eliminating the bias caused by earlier death due to preexisting disease,
4. Determined deaths during a maximum follow-up of 10 years.

RESULTS [2]

1. Men: A subgroup of men who had never smoked, based on BMI at age 50: (n = > 55 000; > 4000 deaths)
    A. The lowest relative risk of death (RR = 1.00) occurred between BMI 22.5 and 24.5

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

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

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

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

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

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

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

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

3. "We observed a J-shaped relation between BMI at the age of 50 and the risk of death in both men and women, with a trend toward increased risk across the entire range of overweight and obese categories."
4. The association between obesity and risk of death was stronger in the last 5 years of observation than in the first 5 years.
5. Excess weight accounted for approximately 18% of all premature deaths in men who had never smoked, and 19% of premature deaths among women who had never smoked.

DISCUSSION

1. "In this large prospective study, obesity (BMI > 30) was strongly associated with the risk of death in both men and women, in all racial and ethnic groups, and in all ages."
2. After accounting for the potential bias owing to preexisting disease and residual confounding by smoking status by using midlife BMI values and restricting the analysis to participants who had never smoked, even moderate elevations of BMI (25.0 to 30.0) conferred an increased risk of death.
3. The risk of death among participants who were overweight (BMI 25 to 30) at age 50 was 20 to 40 percent higher than among participants who had a BMI of 23.5 to 24.9 at age 50. The risk of death also *increased* as BMI declined from about 22.5 to 18.5 in men (18.5 is also included as a "normal" weight.) The authors did not comment on any possible reason for this.
4. The study also adjusted other factors to minimize the effect of possible confounders: education level, race, ethnicity, alcohol consumption, and physical activity. However, "We cannot conclude with complete certainty that the relation between adiposity and the risk of death is causal".
5. Medical complications of obesity include hypertension, insulin resistance, lipid abnormalities, hormonal alterations, and chronic inflammation. All are related to increased risk of death.
6. Many of the subjects included in this study are in the "baby boom" generation.

CONCLUSION

Excess body weight, including overweight (BMI 25 to 30) is associated with an increased risk of death.

NEJM August 24, 2006; 355: 763-78 Original investigation, first author Kenneth F Adams, National Epidemiology Branch, National Institutes of Health, Bethesda MD.

1 Weight in kg / height in meters^2

2 My calculations from their figures 1 page 769 and figure 2 page 774

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

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

In patients *with* left heart failure or with low ejection fractions, angiotensin-converting enzyme inhibitors (**ACE-i)** reduce mortality and morbidity, hospital admissions for heart failure **(HF),** and myocardial infarction **(MI). T**hese benefits are seen in patients with normal blood pressure as well as in patients with hypertension. It has been postulated that the benefit of ACE is likely to be independent of BP lowering.

This study computed cardiovascular outcomes and total mortality reported by 3 large studies of over 29 000 patients with established vascular disease, but without HF or left ventricular systolic dysfunction.

Conclusion: ACE reduced vascular events in these patients.

STUDY

1. The studies compared three different ACE-i: perindopril, trandolapril, and ramipril, with placebo.
2. All subjects had a history of cardiovascular disease: previous myocardial infarction (MI), stroke or ischemic attack, coronary bypass surgery (**CABG),** and peripheral arterial disease. Some had hypertension and diabetes. None had HF or left ventricular systolic dysfunction. (**LVSD**)
3. Many were taking other drugs; antiplatelets, beta-blockers, lipid lowering agents; diuretics, and calcium blockers.
4. Follow-up a mean of 4.5 years.

RESULTS

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

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

10.7 12.8

3. The NNT for 4.5 years to prevent one composite outcome = 48.

DISCUSSION

1. "This review of large trials with a total of 29 805 patients without known LVSD or heart failure, shows clear benefits for the use of ACE inhibitors for a range of outcomes."
2. These results are consistent with 5 previous trials of patients *with* LVSD in which ACE-i improved outcomes.
3. "In view of the broad populations that could benefit, the public health and clinical benefits are important."
4. There were clear benefits when ACE-i were added to other cardiovascular drugs with proven benefits.
5. "Use of ACE inhibitors should be considered in all patients with atherosclerosis." **1**

CONCLUSION

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

Lancet, August 12,2006; 368: 581-88 Original investigation, first author Gilles R Dagenais, Laval University, Quebec, Canada.

1 This is a stretch.

An editorial in this issue of Lancet (pp 555-56), first author Giuseppe Remuzzi, Mario Negri Institute, Bergamo, Italy comments:

"Angiotensin-converting enzyme inhibitors have the broadest effect of any drug in cardiovascular medicine, reducing risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure or left ventricular dysfunction, and patients after myocardial infarction or with peripheral vascular disease, diabetes, stroke, or transient ischemic attack. Furthermore, ACE inhibitors slow or prevent the progression to end-stage renal disease in patients with diabetic and non-diabetic chronic nephropathies, and reduce the risk of nephropathy in those with diabetes and no evidence of renal disease."

Another Application of the Delayed Prescription

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

How effective is topical treatment for acute conjunctivitis? A Cochrane review showed a marginal benefit.

This study assessed the effect of different prescribing strategies for chloramphenicol eye drops in adults and children with acute infective conjunctivitis.

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

STUDY

1. A pragmatic, open, randomized, controlled trial in 30 general practices compared:

   1) immediate antibiotic (chloramphenicol eye drops), 2) delayed antibiotic, or 3) no antibiotic (controls), in over 300 patients with acute infective conjunctivitis.

2. No patient was under age 1, had blocked tear ducts, was systemically unwell, had received antibiotics within 2 weeks, or had a chronic eye infection.
3. The immediate antibiotic eye drops were prescribed every 2 hours for 2 days, then 4 times daily. Delayed antibiotics were provided by a prescription to be picked up at the physician's office at the patient's discretion after 3 days.
4. Primary outcome = duration of moderately bad symptoms, mean symptom severity score on days 1-3, and belief in the effectiveness of the antibiotic.

RESULTS

1. Outcomes:

Use of antibiotic:	Immediate	Delayed	No antibiotic
Actually filled prescriptions	99%	53%*	30%**
Mean symptom score on days 1-3 (7 point scale)	1.9	2.0	2.1
Mean duration (days) of moderate symptoms	3.3	3.9	4.8
No. (%) who believed antibiotics are very effective	67	55	47
No. (%) who are very likely to re-attend for the same Infection	68	41	40

*(*Note that about half of the patients never filled the prescription. **These patients must have re-consulted for their conjunctivitis. A delayed prescription given at the first consultation would prevent this.)*

2. The average score of severity of symptoms days 1-3 did not differ significantly between groups.
3. The immediate group was more likely to believe that antibiotics were effective, and were more likely to state they would re-attend for future conjunctivitis.
4. Outcomes in the delayed group and the control group were not significantly different.
5. Significant bacterial growth was evident in 50% of swabs taken (69 of 138). No significant difference in outcomes between those positive and negative.
6. There was no difference between groups in cure rate at day 8.

DISCUSSION

1. Delaying antibiotics for conjunctivitis in primary care was associated with similar severity and duration of symptoms and with reduced antibiotic use.
2. Belief in the effectiveness of the antibiotic was higher in the immediate group. Intention to re-attend for any possible recurrence was also higher.
3. Antibiotic was used by 53% of the delayed prescription group, and 30% of the controls. This was probably related to a belief of patients in the delayed group of the need for antibiotic despite symptoms being mild. "Whatever the reasons, no initial offer of antibiotics resulted in significant use of antibiotics."
4. Immediate prescribing seemed to medicalize patients. This group was more likely to re-attend if

the eye infection recurred. (They were more convinced that antibiotics cured the infection and would be again needed for treatment.)

5. Delayed prescribing enables the clinician to discuss the clinical course of conjunctivitis with the patient.
6. Patient's lack of the self-limiting nature of conjunctivitis was an important reason for attending for antibiotics.
7. Patients were happy with delayed prescriptions and with deciding whether to start the antibiotic.

CONCLUSION

Delayed prescribing in primary care reduced antibiotic use, showed no evidence of medicalization, and provided similar duration and severity of symptoms.

BMJ August 12, 2006; 333: 321-24 Original investigation, first author Hazel A Everitt, University of Southhampton, UK

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

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

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

CA-MRSA has been described primarily as a cause of skin and soft tissue infections. It has also been associated with sepsis and necrotizing pneumonia.

As compared with health-care associated MRSA, CA-MRSA isolates tend to be sensitive to more antibiotics and to produce different toxins. They have different types of the gene complex which confers methicillin resistance. This study determined the prevalence of MRSA as a cause of skin infections among community dwelling adults presenting to EDs in several geographically diverse metropolitan areas

Conclusion: CA-MRSA was the most common identifiable cause of skin and soft tissue infections.

STUDY

1. Prospective prevalence study involved community-dwelling adults (median age 39; 2/3 male) with skin and soft tissue infections presenting to hospital EDs in 11 different U.S. cities during one month in 2004. All were age 18 and over; all had purulent skin and soft tissue infections of less than one week's duration.
2. All were cultured. Antimicrobial susceptibility was determined by a panel of agents routinely used to determine resistance.

RESULTS

1. Classifications of infections:	Type of infection	MRSA isolated
Abscess	81%	61%
Purulent wound	11%	53%
Cellulitis with purulent exudate	8%	47%

2. MRSA was isolated from 59% of all patients. It was the most common identifiable cause.

3. MRSA susceptibility:	%
Trimethoprim-sullfamethoxazole	100
Rifampim	100
Clindamycin	95
Tetracycline	92
Fluoroquinolones	60
Erythromycin	6

4. Potential risk factors for CA-MRSA	Odds Ratio
Non-Hispanic black	1.9
Use of any antibiotic in past month	2.4
Reported spider bite (vs. other cause)	3.0
Close contact with person with similar infection	3.8

5. In 100 of 175 MRSA infections for which antibiotics were provided, 57% were *not* concordant with results of susceptibility testing.
6. At day 17 after the ED visit, 96% of patients reported that their infection had resolved or improved.
7. There was no difference in outcome between those infected with CA-MRSA and those infected with other bacteria, or between those whose CA-MRSA was resistant and those whose CA-MRSA was sensitive to the antibiotic prescribed.

DISCUSSION

1. There has been a dramatic trend of increased prevalence of CA-MRSA in the past few years. It has emerged as the most common identifiable cause of skin and soft tissue infections.
2. The great majority of patients received empirical antimicrobial therapy. Of these, 57% of the infecting organism was resistant to the antibiotic prescribed. "This suggests need to reconsider empirical antimicrobial choices for skin and soft tissue infections."
3. Most patients in this study were treated with beta-lactam agents such as cephalexin and dicloxacillin, to which their CA-MRSA infections were not susceptible. However, there was no association between patient's outcomes and susceptibility of the organism to the antimicrobial used. This suggests that most CA-MRSA infections can be cured with adequate drainage. The susceptibility of a given pathogen to prescribed antimicrobial agents may be more likely to affect the outcome among patients with cellulitis or purulent wounds.
4. The combination of rifampim with trimethoprim-sullfamethoxazole has been suggested for the treatment

of purulent infections with CA-MRSA

5. Clinicians should consider CA-MRSA in patient reporting a spider bite.
6. Further transmission of the infection may be facilitated by keeping lesions covered by clean dry bandages, practicing good hand hygiene, and avoiding sharing contaminated items.
7. The high prevalence of CA-MRSA has implications for hospital policies regarding infection control.
8. Clinicians should consider obtaining cultures from patients with skin and soft tissue infections, and modifying standard empirical therapy to provide CA-MRSA coverage when antibiotics are indicated.
9. Trends in antimicrobial sensitivity of CA-MRSA must be followed to identify optimal therapy.

CONCLUSION

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

NEJM August 17, 2006; 355; 666-74 Original investigation, first author Gregory J Moran, Olive View-UCLA Medical Center, Sylmar, CA.

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"Potentially Pose A Nightmare Scenario"

8-7 THE TREATMENT TRIANGLE FOR STAPHYLOCOCCAL INFECTIONS

A reassessment about how to best treat staph infections is occurring because of:

1) The decline in the development of new antibiotics.
2) The recognition that partial vancomycin resistance may result in some vancomycin treatment failures among methicillin-resistant staphylococcus aureus (**MRSA**) infections.
3) The emergence of community-associated MRSA strains that are unrelated to earlier strains. (Numerous community-associated MRSA have been identified worldwide.)

New community-acquired MRSA (**CA-MRSA**) are highly virulent. They cause skin and soft-tissue infections and necrotizing pneumonia in otherwise healthy adults and children.

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

The preceding article defines the amazing extent to which CA-MRSA has spread through the U.S. population. Over 50% of skin and soft tissue infections seen in emergency departments were caused by CA-MRSA. In this study, almost all were susceptible to trimethoprim-sullfamethoxazole, rifampim, clindamycin, and tetracycline. About 60% were susceptible to fluoroquinolones; only 6% were susceptible to erythromycin.

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

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

1) Drainage and debulking

2) Wound culture

3) Antibiotic therapy

The weight is on drainage and debulking.

CA-MRSA are *not* usually multi-drug resistant. MRSA associated with health care are usually multidrug-resistant. In vitro susceptibility to vancomycin, rifampim and linezolid should be assessed in the hospital setting.

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

NEJM August 17, 2006; 355: 724-27 Editorial by M Lindsay Grayson, University of Melbourne, Australia.

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Harm Outweighs Benefit

8-8 CELECOXIB FOR THE PREVENTION OF SPORADIC COLORECTAL ADENOMAS

Drugs that inhibit the enzyme cyclo-oxygenase-2 (COX-2 inhibitors; **COX-2 i**) reduce the number of colorectal adenomas in patients with familial adenomatous polyposis. This suggests that COX-2 i may also prevent sporadic colorectal adenomas.

This trial randomized over 2000 subjects to: 1) COX-2 inhibitor celecoxib (*Celebrex*) 200 mg twice daily, or 2) 400 mg twice daily, or 3) placebo for 3 years. All had adenomas removed before study entry.

Repeat colonoscopies were performed at 1 and 3 years. Compared with placebo, celecoxib reduced rate of recurrent adenomas by about 20%

Adverse events were more common in the celecoxib groups.

	Placebo	200 mg	400 mg
Cumulative incidence of adenomas at 3 years:	61%	43%	37%
Serious cardiovascular events	1%	2.6%	3.4%
Serious cardiovascular events in patients with history of cardiovascular disease at baseline	3%	9%	9%

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

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

NEJM August 31, 2006; 355: 873-84 Original investigation by the Adenoma Prevention by Celecoxib (ADP) study, first author Monica M Bertagnolli, Brigham and Women's Hospital Boston Mass.

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As Effective and As Safe As LMWH. Suitable for Outpatient Treatment.

8-9 COMPARISON OF FIXED-DOSE WEIGHT-ADJUSTED UNFRACTIONATED HEPARIN AND LOW MOLECULAR-WEIGHT HEPARIN FOR ACUTE TREATMENT OF VENOUS THROMBOSIS.

Deep vein thrombosis **(DVT)** and pulmonary embolism **(PE)** are usually treated with a minimum of 5 days of heparin overlapped with warfarin for at least 3 months.

Unfractionated heparin, given by intravenous (**i.v.)** infusion with dose-adjustments according to activated partial thromboplastin time (**APPT**) has been standard. Low-molecular-weight heparin (**LMWH**) given subcutaneously (**s.c.)** in fixed, weight-adjusted dose is gradually replacing i.v. heparin. Subcutaneous administration without laboratory monitoring makes the LMWH treatment available for out-patient use.

APPT measurements are of uncertain clinical relevance in patients being treated with heparin because they differ depending on the reagents and coagulometers used. Warfarin increases APPT. APPT has an uncertain relationship to efficacy and safety.

This trial was designed to determine if fixed-dose weight-adjusted unfractionated heparin given s.c is as effective and safe as LMWH in treatment of VTE.

Conclusion: It is as safe and as effective. It is suitable for outpatient treatment.

STUDY

1. Randomized, non-inferiority trial followed over 700 patients (mean age 60) with acute VTE. All had newly diagnosed VTE confirmed by venography or ultrasonography, or pulmonary embolism confirmed by CT angiography.
2. Randomized to:
   1) Unfractionated heparin given s.c.—initial dose = 333 U/kg; followed by 250 U/kg every 12 hours.
   2) LMWH (dalteparin or enoxaparin) given s.c at a dose of 100 IU/kg every 12 hours.
3. No coagulation tests were used to modify doses.
4. Both drugs were administered for at least 5 days. Both were overlapped with warfarin, usually started on the first day as heparin, and continued for at least 5 days. Most subjects were treated as outpatients.
5. Main outcome = recurrent VTE and major bleeding.

RESULTS

1. Recurrent VTE	Unfractionated heparin (n = 345)	LMWH (n = 352)
Three months	13 patients (3.8%)	12 patients (3.4%)
DVT recurrence	11 patients	8 patients
PE	2 patients	4 patients.
Deaths 3 months	5.2%	6.3%

2. Major bleeding (1st 10 days) 1.1% 1.4%

DISCUSSION

1. "Fixed-dose, unmonitored, subcutaneous unfractionated heparin is as effective and safe as low-molecular-weight heparin in patients with acute venous thromboembolism."
2. This study provides evidence that APPT monitoring is not required with this dosing regimen.
3. Unfractionated heparin given s.c is suitable for outpatient use.
4. Unfractionated heparin is much less costly than LMWH ($ 0.15 for 1000 U vs $7.42 for 1000 IU of enoxaparin; ($37 vs $712 for a 6-day course in a 80 kg patient.)

CONCLUSION

Fixed-dose subcutaneous heparin was as effective and as safe as LMWH for initial treatment of venous thromboembolism. It is suitable for treatment of outpatients.

JAMA August 23/30 206; 296: 935-42 Original investigation, first author Clive Kearon, McMaster University, Hamilton, Ontario, Canada.

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Associated With Reduced Risk Of Rupture Of AAA

8-10 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND AORTIC RUPTURE

Abdominal aortic aneurysms (**AAA)** develop in over 4% of men and in over 1% of women above age 50. About 1/3 of untreated AAA rupture. Rupture is highly lethal. Surgery also carries a mortality and often results in compilations. To date, no medical treatment has been shown to prevent AAA or to forestall need for surgery.

Activation of the renin-angiotensin system has been implicated in the genesis of heart failure, hypertension, and atherosclerosis. Emerging evidence links the system to AAA as well. Angiotensin II is strongly upregulated in human aortic aneurysms with increases mediated through pathways dependent on angiotensin converting enzyme.

Animal studies suggest that ACE-inhibitors (**ACE-i**) might slow the progression of AAA and prevent expansion and rupture. Such protection was not apparent for angiotensin II blockers, calcium blockers, or hydralazine. This suggests that the mechanism involved might *not* be related to lowering of BP.

This population-based study postulated that ACE-i would reduce risk of rupture.

Conclusion: ACE-i were associated with a reduced risk of rupture.

STUDY

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

3. Compared use of ACE-i in both groups (primarily lisinopril, enalapril, and ramipril), defined as two or more prescriptions in the year before, with at least one prescription in the 3 months immediately preceding admission.
4. Very few patients had contraindications to ACE-i: hyperkalemia, angioedema, hypotension, and renal artery stenosis.
5. Computed the association between use of ACE-i and aortic rupture.

RESULTS

1. Patients who had received ACE-i before admission were less likely to present with rupture. (Odds ratio = 0.82.)
2. Rupture: Taking ACE-i (n = 665) Not taking ACE-i (n = 2761)
   133 (20%) 635 (23%)
   (Difference = 3% NNT to prevent one rupture = 33.)
3. Patients who were prescribed ACE-i but discontinued during the 3 months before admission were not protected. (The mean time between the last prescription and hospital presentation in this group was 6 months.)
4. No protective associations were evident for beta-blockers, calcium blockers, alpha blockers, or thiazides,

DISCUSSION

1. In patients with AAA, ACE-inhibitors were associated with a reduced risk of rupture. This association was maintained after adjustment for many confounders.
2. This effect was distinct and not apparent for other antihypertension drugs or for drugs linked to preventive health care. (Eg, statins)
3. The protective benefit was not evident in patients who had discontinued ACE-i within the preceding 6 months.
4. Possible biological pathways for the effect:
   1) Provision of angiotensin II to animals increase aortic stiffness and reduces elastin content. These effects are reversed by ACE-i.
   2) In patients with established AAA, ACE-i (but not other antihypertension drugs) augment systemic collagen synthesis and reduce stiffness of the aortic wall.
   3) Under ACE inhibition, arterial compliance improves.
   4) ACE-i, in humans, reduce vascular inflammation, and increase elastin deposition,
5. Some of these mechanisms also apply to angiotensin receptor blockers. Because of the small numbers of patients in the sample, these investigators were not able to ascertain whether the benefits extend to angiotensin II blockers.
6. Hypertension is a risk factor for AAA, yet control of hypertension is often not sufficient for stabilizing the aneurismal wall.

7. In randomized trial of patients with AAA, propanolol (a beta-blocker) lowered BP, but did not affect expansion of the aneurysms. This trial found no association between beta-blockers and many other antihypertension drugs and risk of rupture.
8. "ACE inhibitors might be distinct in affecting the pathology of abdominal aortic aneurysms."

CONCLUSION

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

Lancet August 19, 2006; 368: 659-65 Original investigation, first author Daniel G Hackham, University of Toronto, Canada.

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"The Reduction In The Risk Of Fatal Stroke Was Consistent With The Treatment Effect, but Not Significant."

8-11 HIGH-DOSE ATORVASTATIN AFTER STROKE OR TRANSIENT ISCHEMIC ATTACK

Statin drugs reduce the incidence of strokes among patients with increase risk factors for cardiovascular disease. Do they also reduce risk of a recurrent stroke after a first stroke or after a transient ischemic attack? **(TIA)**

This randomized trial compared the effect of high dose atorvastatin (*Lipitor*) vs placebo on risk of stroke after a first episode. (Secondary prevention.)

Conclusion: Among patients with no known coronary heart disease, high dose atorvastatin, compared with placebo, slightly reduced risk of ischemic stroke and major cardiovascular events over 5 years. Risk of hemorrhagic stroke was increased. Mortality was not decreased.

STUDY

1. Randomized over 4700 patients (mean age 63) to: 1) Atorvastatin 80 mg daily, or 2) Placebo.
2. All patients had a stroke or TIA within 6 months of entry. None had known coronary heart disease. Patients with atrial fibrillation were excluded.
3. At baseline, LDL-cholesterol levels were 100 to 190 mg/dL. (Mean = 133.)
4. At baseline, mean body mass index = 27; 19% were current smokers; 62% had hypertension; 16% had diabetes. Mean LDL-c was 133; mean HDL-c was 50.
5. Many were taking other cardiovascular drugs: aspirin; ACE-inhibitor; beta-blocker; angiotensin II blocker; calcium blocker.
6. Median follow-up = 5 years.

RESULTS

1. Mean lipid values during course of the trial	Atorvastatin (n = 2365)	Placebo (n = 2366)
LDL-c	72 mg/dL*	128 mg/dL
HDL-c	52	51
Triglycerides	115	145

(* *Note that high dose did not lower LDL to below 70, the recommended target level.)*

2. Stroke over 5 years (primary outcome)		
Non-fatal stroke	10.4 %	11.8 %
Fatal stroke	1.0 %	1.7 %
(NNT to prevent one non-fatal stroke in 5 years = 71; to prevent one fatal stroke = 143)		
3. Overall mortality (number of deaths)	216	211
4. Number of patients with hemorrhagic stroke	55	33
(Ie, no reduction on overall mortality; and an increase in hemorrhagic stroke.)		
5. Elevation of liver enzymes	2.3%	0.5%
6. Any adverse event resulting in discontinuation of study treatment	17.5%	14.5%
7. Other cardiovascular events: (*not a primary end-point*)		
Non-fatal MI	1.8%	3.3%
Acute coronary event	4.3%	6.4%
Revascularization	4.0%	6.9%

DISCUSSION

1. "The reduction in the risk of fatal stroke was consistent with the treatment effect, but not significant."
2. In patients who had no known coronary heart disease at baseline, the risk of cardiovascular events and revascularization procedures was reduced.
3. "The overall benefits in terms of the reduction in the risk of stroke was significant despite an increase in hemorrhagic stroke in the atorvastatin group."
4. The beneficial effect of statins on risk of recurrent stroke has been attributed largely to a reduction in the risk of cerebral infarction, which has been attributed to a reduction in LDL-c.
5. "The risk of recurrence (of stroke) is highest in the first year after stroke."
6. "Our results support the concept that, from the standpoint of statin treatment, stroke or TIA should be considered a coronary heart disease risk equivalent. " "The potential risk of recurrent hemorrhage should be considered when one is deciding whether to administer a statin to patients who have had a hemorrhagic stroke."

CONCLUSION

In patients with a recent stroke or TIA and without known coronary heart disease, 80 mg of atorvastatin over 5 years slightly reduced overall incidence of stroke and cardiovascular events, despite a small increase in the incidence of hemorrhagic stroke.

NEJM August 10, 2006; 355: 549-59 Original investigation by the Stroke Prevention by Aggressive Reduction in Cholesterol levels (SPARCL) investigators, first author Pierre Amaerenco, Denis Diderot University, Paris, France.

An editorial in this issue of NEJM (pp 613-15) by David M Kent, Tufts-New England Medical Center, Boston Mass comments:

Perhaps underlying the less certain or less consistent role of cholesterol level and the risk of stroke than in heart attack is that strokes are much more heterogeneous, and only a minority of strokes are caused by large-vessel athero-thrombosis.

Embolic strokes related to atrial fibrillation were excluded from the trial. These strokes are less likely to be responsive to cholesterol lowering drugs. “This raises the issue whether the results of this trial apply to the roughly one in five ischemic strokes that are of cardiac origin.”

There is epidemiological evidence for an association between increased risk of intracerebral hemorrhage and (lower) cholesterol levels. Statins have antithrombotic effects. Why did the trial consider a hemorrhagic stroke a qualifying event for entry? (About 2% of study patients had a hemorrhagic stroke.) Atorvastatin was associated with an increase in hemorrhagic stroke over 5 years.

Regardless of the modest benefits of atorvastatin, the editorialist believes it likely that adoption of statin therapy will be included in discharge guidelines for patients with ischemic stroke.

In the past year, *Practical Pointers* has abstracted several articles regarding use of high dose statins

1 BMJ June 3, 2006; 332: 1330-32 Editorial “Should We Lower Cholesterol as Much as Possible?” *Practical Pointers* June 2006 [6-4]

Adverse effects of statins are underreported, and benefits of higher doses may be exaggerated.

2 “High Dose Atorvastatin vs Usual Dose Simvastatin for Secondary Prevention after Myocardial Infarction: JAMA November 4, 2005; 294: 2437-45 *Practical Pointers* November 2005 [11-8]

Over 5 years there was no difference in outcomes. Adverse events and withdrawals were more common in the atorvastatin group

3 “Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease” NEJM 2005; 294: 2337-45

Atorvastatin associated with greater increase in adverse effects, withdrawals, and increase in liver enzymes.

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An Emerging, Simple Marker of Kidney Function

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

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

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

Levels are independent of weight and height, muscle mass, age, and sex (in contrast to creatinine clearance). Measurements can be made from a single random blood sample. Cystatin C identifies a “pre-clinical” state of kidney dysfunction that is not detected by serum creatinine or estimated GFR.

Cystatin C is becoming increasingly available. It is superior to serum creatinine alone in estimating kidney function. Elevated serum levels (above 1 mg/L) have been considered a marker for “pre-clinical” kidney disease, especially in the community-dwelling elderly. High levels have been associated with an increased risk of cardiovascular disease and death. Cystatin C provides better prediction than creatinine. Increased levels may help to improve targeting of preventive strategies such as lipid control and tailored anti-hypertension treatments.

The cystatin C assay is approved by the FDA for diagnostic testing of decreased kidney function. Availability is still limited. It is expensive. Different assays have different calibration. There are potential non-renal influences that may affect serum levels. Despite these problems, cystatin C represents renal function better than creatinine.

Albuminuria is also a marker of kidney dysfunction. About 20% of adults over age 70 have microalbuminuria (albumin-to-creatinine ratio 30 to 299 mg/g). Another 3% have albuminuria (a-t-c ratio 300 mg/g and above) on a single spot urine sample. It is correlated with a decreased GFR, and is a strong risk factor for cardiovascular disease and death.

This abstract is based on several sources:

1 Annals Int Med August 15, 2006; 145: 247-254 "Using Standard Serum Creatinine Values in the Modification of Diet in Renal Disease Study for Estimating Glomerular Filtration Rate" first author Andrew S Levey, Tufts-New-England Medical Center, Boston Mass.

2 Annals Int Med August 15, 2006; 145: 237-246 "Cystatin C and Prognosis for Cardiovascular and Kidney Outcomes in Elderly Persons without Chronic Kidney Disease" first author Michael Shlipak, University of California, San Francisco.

3 Annals Int Med august 15, 2006; 145: 299-300 "Decreased Kidney Function in the Elderly" Editorial, first author Josef Coresh, Johns Hopkins University, Baltimore MD:

4 The Internet

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You May Set Off The Alarm and Be Strip-searched

You Should Avoid Conceiving for A Year

8-13 TRIGGERING RADIATION ALARMS AFTER RADIOIODINE TREATMENT. [1]

WHAT TO TELL PATIENTS ABOUT RADIOIODINE THERAPY [2]

Increasing numbers of diagnostic and therapeutic procedures involving radioisotopes are being conducted. The most common are; thallium scans for myocardial perfusion, ventilation-perfusion lung scans, iodine uptake scans, and radioactive treatment of thyroid disorders.

These procedures make patients temporarily radioactive. By activating the ever more sensitive radiation detectors, false alarms in airports maybe triggered. Patients and doctors may not be aware of this risk, and the potential problems it may produce.

This article reports a case of a 46 year old man who was treated with ^{131}I for thyrotoxicosis.
The patient received a card highlighting the usual precautions to be taken. It did not mention the risk of radiation detectors being triggered.

Six weeks after the treatment, he set off a detector in an airport. He was immediately detained and strip-searched. A prolonged period of interrogation ensued. Fortunately, he was carrying his radionuclide card with him. After long delay and much embarrassment, he was released.

This potential problem has not been adequately communicated to patients even by staffs in nuclear medicine. It has not been described adequately in the literature.

Number of days up to which patients might trigger alarms:

Fluoride-18	1
Technicium-99m	3
Indium-111	14
Gallium-67	30
Thallium -201	30
Iodine-131	95

An accompanying article suggests several precautions for patients receiving radioiodine therapy

Avoid risking conception for at least 4 months (both male and female patients) in order to reduce risk of radiation to the fetus. (The American Thyroid Society recommends up to 1 year.) Patients may be informed that after this time there is no evidence of risk of genetic abnormalities.

Inform men that a reduced sperm count may occur and cause temporal infertility for up to 2 years.

Avoid prolonged daily close contact (1 meter) with children for the time dependent on the dose of radioiodine received.

Avoid public transport for 2 weeks so as not to expose nearby passengers.

Long term follow-up shows no increase in risk of cancer.

Hypothyroidism is the only long term risk. All patients should be warned that they might require life-long thyroxine replacement.

Despite the constant half-life of ^{131}I of 8 days, its effective half-life varies widely with the patient's renal function. The only practical solution is to adequately counsel anyone receiving any radioisotope, and to advise them to carry a radiation certificate.

1 BMJ August 5, 2006; 333: 293-94 "Lesson of the Week", commentary, first author Kalyan Kumar, City Hospital Birmingham, UK

2 BMJ August 5, 2006; 333: 271-72 Editorial, first author Daniel J Cuthbert son, Ninewells Hospital and Medical School, Dundee, UK