

PRACTICAL POINTERS

FOR PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

FEBRUARY 2003

OTTAWA ANKLE RULES EXCLUDE FRACTURES OF THE ANKLE AND REDUCE NEED FOR X-RAY

ARE ACE INHIBITORS BETTER THAN DIURETICS FOR HYPERTENSION IN THE ELDERLY?

INITIAL TREATMENT OF HYPERTENSION: WHAT DRUG(S) TO USE?

THE PREVENTION AND TREATMENT OF JET LAG: IS MELATONIN REALLY EFFECTIVE?

IBUPROFEN BLOCKS THE CARDIOPROTECTIVE EFFECT OF LOW-DOSE ASPIRIN

SHOULD WE SCREEN FOR HUMAN PAPILLOMA VIRUS DNA TO DETECT CERVICAL-CANCER?

SALMETEROL + FLUTICASONE BETTER THAN EITHER ALONE IN THE TREATMENT OF COPD

LOW-TO-MODERATE ALCOHOL CONSUMPTION REDUCES RISK OF ISCHEMIC STROKE

CARVEDILOL IS EFFECTIVE TREATMENT FOR SEVERE CHRONIC HEART FAILURE

LOWER SERUM DIGOXIN CONCENTRATIONS IMPROVE OUTCOMES IN HEART FAILURE

PACEMAKER CARDIAC RESYNCHRONIZATION REDUCES DEATH FROM HEART FAILURE

PANEL INDORSES LIMITED ROLE FOR C-REACTIVE PROTEIN TESTING

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

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HIGHLIGHTS FEBRUARY 2003

2-1 ACCURACY OF OTTAWA ANKLE RULES TO EXCLUDE FRACTURES OF THE ANKLE AND MID-FOOT

- 1) Inability to bear weight and walk 4 steps immediately after the injury, or on presentation to the emergency department.
 - 2) Bony tenderness localized to the posterior edge (and up to 6 cm above) either malleolus (four spots).
- Fewer than 2% of patients negative for fracture by the rules actually had fracture.

Application of the rules greatly reduces the number of X-rays taken.

2-2 A COMPARISON OF OUTCOMES WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS AND DIURETICS FOR HYPERTENSION IN THE ELDERLY. .

Initiation of antihypertension treatment with ACE inhibitor in *older men* appeared to lead to better outcomes than diuretics despite similar reductions of BP. Patients often required 2 or more drugs.

NNT to benefit one male patient over 1 year = 270. No benefit in females.

2-3 INITIAL TREATMENT OF HYPERTENSION

On the basis of available data, diuretics or beta-blockers remain appropriate for the initial treatment of uncomplicated hypertension.

“In patients over age 65, morbidity and mortality from cardiovascular disease are reduced when systolic blood pressure is lowered to a level below 160 mm Hg. Whether levels below 140 mm Hg provide additional protection is unclear.”

“Optimal blood pressure targets remain to be determined, particularly for elderly patients.”

Primary care clinicians should develop a set initial drug protocol for treating long standing (ie, lifetime) illnesses which require long-term costly medication. We should aim to provide the least expensive, least toxic drugs and drug doses, which are easiest to take, and more likely to lead to compliance. The editor of *Practical Pointers* suggests a protocol.

2-4 THE PREVENTION AND TREATMENT OF JET LAG.

The Cochrane Review concludes that 2 to 5 mg melatonin taken at bedtime at the new destination is effective, and may be worth repeating for the next two to four days.

The article gives other suggestions for minimizing both travel fatigue and jet lag.

2-5 EFFECT OF IBUPROFEN ON CARDIOPROTECTIVE EFFECT OF ASPIRIN

Ibuprofen negates the protective effect of low dose aspirin. Use another NSAID.

2-6 ADDING A TEST FOR HUMAN PAPILLOMA VIRUS DNA TO CERVICAL-CANCER SCREENING

Virtually all squamous-cell cervical carcinomas contain one of eighteen types of human papilloma virus (HPV). The relative risk of cervical cancer associated with persistent infection with high-risk types of HPV (*especially types 16 and 18*) is higher than the risk of lung cancer associated with smoking.

The discovery that *continued presence* of tumor-producing HPV is necessary for development of cervical cancer is revolutionizing our approaches to screening and prevention. An obvious correlative is that the absence of infection means that the risk of cervical cancer is negligible.

2-7 COMBINED SALMETEROL AND FLUTICASONE IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Combined inhaled long-acting beta agonist/corticosteroid produced better control of symptoms and lung function than the use of either component alone, with no greater risk of adverse effects.

“This combination treatment should be considered for patients with COPD.”

2-8 ALCOHOL CONSUMPTION AND RISK OF STROKE: A Meta-analysis

Heavy alcohol consumption increases risk of stroke. Light-to-moderate consumption protects against ischemic stroke, but not against hemorrhagic stroke.

2-9 EFFECTS OF INITIATING CARVEDILOL IN PATIENTS WITH SEVERE CHRONIC HEART FAILURE

Benefits of beta-blocker therapy with carvedilol were evident within a few weeks in patients with advanced HF who were euvolemic. Benefits were similar to those obtained by long-term therapy.

Initiation of treatment was well tolerated when a go-slow, go-low dose was used.

2-10 ASSOCIATION OF SERUM DIGOXIN CONCENTRATION AND OUTCOMES IN PATIENTS WITH HEART FAILURE

Higher serum concentrations of digoxin were associated with increased mortality in patients with HF who were in normal sinus rhythm. The most effective concentration may be 0.5 to 0.8 ng/mL .

2-11 CARDIAC RESYNCHRONIZATION AND DEATH FROM PROGRESSIVE HEART FAILURE

Recently, cardiac pacemakers have been modified to correct ventricular dyssynchrony (left bundle branch block). The new pacemakers use a left ventricular lead that ensures stimulation of the left ventricle at, or near, the time of right ventricular depolarization. Synchronization enhances cardiac function and reduces myocardial oxygen consumption. It improves exercise capacity, functional class, and quality of life.

Use of the pacemaker was associated with a reduction in mortality from 3.5% to 1.7% over 6 months among patients with advanced HF.

2-12 PANEL INDORSES LIMITED ROLE FOR CRP TESTS

C-reactive protein (CRP) has emerged as the leading inflammatory marker for cardiovascular disease.

Does the test add anything to the list of risk markers now available? How should it be used?

A guideline suggests that CRP has its greatest utility in people deemed at intermediate risk of CVD. (intermediate risk = 10% to 20% risk of developing CVD in the next 10 years as calculated from the Framingham risk score.) Physicians should assess traditional risk factors and calculate the absolute Framingham risk score before testing with CRP.

<http://hin.nhlbi.nih.gov/atp/iii/calculator.asp?usertype=prof> .

CRP should not be used routinely, or as an alternative to traditional risk factor assessment. It is not known if an elevated CRP as the sole risk marker needs treatment.

If You Can Walk, And Have No Bone Tenderness—No Fracture

2-1 ACCURACY OF OTTAWA ANKLE RULES TO EXCLUDE FRACTURES OF THE ANKLE AND MID-FOOT

Primary care clinicians frequently encounter patients with acute ankle injuries. Even though only about 15% of such injuries are fractures, almost all patients are X-rayed despite the expense and inconvenience. This small yield prompted development of the Ottawa Ankle Rules:

- 1) Inability to bear weight and walk 4 steps immediately after the injury, or on presentation to the emergency department.
- 2) Bony tenderness localized to the posterior edge (and up to 6 cm above) either malleolus (four spots).

Midfoot assessment is added to the ankle rule:

- 3) Inability to bear weight and walk 4 steps immediately after the injury, or on presentation to the emergency department.
- 4) Tenderness of the navicular area or base of the 5th metatarsal.

If both assessments are negative, fracture is unlikely. (*See illustration p 418*)

This study summarizes the evidence of accuracy of the rule as a decision aid.

Conclusion: The rule is an accurate instrument for excluding fracture and lowering the need for X-ray.

STUDY

1. Systematic review of the literature included 27 relevant studies (over 15 000 patients).

RESULTS

1. If the patient actually has a fracture, in how many would the tests be positive (true positive test) and in how many would the tests be negative (false negative test)? (Ie, what is the *sensitivity* of the test?)

Among all who had a fracture, 96.4% to 99.6% had a positive test (true positive).

Sensitivity of the test in determining fracture = 96% to 99%.

Only 0.4% to 3.6% of patients with fracture had a negative test (false negative). Ie, very few fractures would be missed if the patient was able to walk and had no tenderness.

2. If the patient did *not* have a fracture, in how many would the test be negative (true negative test)? (Ie, what is the *specificity* of the test?)

Among all who did *not* have a fracture, the studies reported a wide range of true negative tests.

Specificity ranged from 48% to 26%.

The investigators were surprised at the wide variability. This would indicate that, among those who did *not* have a fracture, many had positive test (false positive). This could indicate a high number of unnecessary X-rays would be performed. The subtlety of palpation technique might explain some of the large variation.

3. Assuming the probability of fracture overall in the cohort of patients presenting with acute ankle injury is less than 15%, fewer than 2% of those with a negative test would have a fracture.
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DISCUSSION

1. Fewer than 2% of patients negative for fracture by the rules actually had fracture.
2. The rule was developed to avoid unnecessary radiography. However, the investigators recognize that use of the test may not change clinical behavior. Clinicians aim to minimize the number of missed fractures (defensive medicine) and would therefore maximize the use of X-ray in order to avoid missing one fracture. Immediate access to X-ray may further trigger requests for X-ray.

BMJ February 22, 2003; 326: 417-19 Original study, first author Lucas M Bachmann, Zurich University, Switzerland. www.bmj.com/cgi/content/full/326/7386/417

Comment:

As the investigators comment, when application of the rule indicated no fracture present, many patients nevertheless received an X-ray. Patients may insist on X-ray. Their physician may readily comply in order to reassure the patient and maintain the doctor-patients relationship. (*This is akin to ordering an ECG for a patient with chest pain even though it is obvious the symptoms do not indicate any cardiac involvement.*) Primary care clinicians may have to talk patients out of having some tests on a basis of cost and inconvenience.

Primary care clinicians have a fall-back strategy. If the rule indicates no X-ray needed, the patient may be advised to rest and avoid any activity which increases pain until the pain abates. If pain continues, a reassessment is indicated. Follow-up by telephone in a day or two will reassure both patient and clinician. RTJ

An accompanying editorial in this issue by John Heyworth (pp 405-06) , Southampton General Hospital , UK comments:

“ An unselective policy has resulted in inestimable numbers of unnecessary exposures to radiation for little diagnostic yield. In addition to being poor medicine, such profligacy is a luxury that is no longer acceptable in any health system.”

In some studies the rules have been 100% accurate, and reduced the number of radiographs by up to 29% without missing any clinically significant fracture.

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No Benefit In Females. NNT in Men = 270 Is This Clinically Significant?

2-2 A COMPARISON OF OUTCOMES WITH ANGIOTENSIN-CONVERTING-ENZYME INHIBITORS AND DIURETICS FOR HYPERTENSION IN THE ELDERLY.

Treatment of hypertension with diuretics, beta-blockers, or both, leads to improved outcomes.

It has been postulated that agents that inhibit the renin-angiotensin system (eg, ACE inhibitors) confer benefit beyond their reduction of BP alone.

This study compared outcomes in older patients with hypertension who were treated with ACE inhibitors vs those treated with diuretics.

Conclusion: Initiation of antihypertension treatment with ACE inhibitor in *older men* appeared to lead to better outcomes than diuretics despite similar reductions of BP.

STUDY

1. Prospective, randomized, open-label trial entered over 6000 subjects with hypertension (age 65 to 84; mean = 72). All were hypertensive (mean BP = 168/91). All were receiving care in family practices. None had recent cardiovascular events.
2. Assigned by randomization to: 1) ACE inhibitor based drug therapy, or 2) diuretic based therapy. The ACE inhibitor enalapril (*Vasotec*; generic) and the diuretic hydrochlorothiazide (*generic*) were recommended as initial therapy, but the specific agent and dose was decided by the family practitioner.
3. At randomization, 83% of subjects in both groups began to receive the designated therapy. At end of study, 62% to 65% were still receiving the assigned therapy; 66% were receiving mono-therapy; up to 6% were receiving three or more drugs.
4. Outcomes: total number of cardiovascular events or death from any cause.
5. Follow-up = mean of 4 years.

RESULTS

1. At end of study, BP declined by 26/12 mm Hg in both groups. Declines were similar in men and women.
2. Cardiovascular events and deaths per 1000 patients years:

ACE group	56.1
Diuretic group	59.8

[Hazard ratio = 0.89 favoring ACE. Absolute difference = 0.37 per 100 persons per year.
NNT(for one year to benefit one patient) = 270
3. Among male patients, the benefits were slightly more evident (hazard ratio favoring ACE = 0.83). There was no benefit for women (hazard ratio = 1.00)
4. A similar number of strokes occurred in each group.

DISCUSSION

1. This study was confined to persons mean age 72 with hypertension (mean BP = 168/91) who were relatively healthy at baseline.
2. Over 4 years, ACE inhibitor therapy was associated with fewer deaths than diuretic therapy only in male subjects; not in females. BP reductions were the same in both groups.
3. Only 60% of subjects continued to receive the drug assigned at baseline. About 1/3 of subjects required 2 or more drugs to reach target BP.
4. The study was conducted in family practices where most elderly receive their care.

CONCLUSION

In elderly male (but not female) subjects with hypertension, ACE-inhibitor-based therapy resulted in an outcome advantage over a diuretic-based regimen, despite similar reductions in blood pressure.

NEJM February 13, 2002; 348: 583-92 Original investigation, first author Lindon M H Wing, School of Medicine, Flinders University, Melbourne, Australia. www.nejm.org

Comment:

Study partially supported by Merck.

Are the results clinically significant? I do not think so. Certainly, not for women. I doubt the relevance of results which do not report benefits in this great a subset of patients.

COST My pharmacy quotes:

Hydrochlorothiazide 50 mg	24 cents each	Pill-cut to 25 mg	12 cents each
Amiloride 5 mg/HCTZ 50 mg	20 cents each	Pill cut to 2.5/25	10 cents each.
Captopril 25 mg	20 cents each		
Captopril 50 mg	20 cents each	Pill cut to 25 mg	10 cents each.

(Generic enalapril is considerably more expensive than generic captopril.)

Fortunately, with availability of generics, costs have come down considerably—important for life-long therapy.

An editorial in this issue (pp 639-41) by Edward D Frohlich, Ochsner Clinic Foundation, New Orleans comments:

“For patients with essential hypertension, but without complications, it makes sense for the prescribing physician to choose a diuretic in a dose that does not cause potassium wasting, precipitate gout, or have other unwanted effects.”

“Both ACE inhibitors and diuretics are extremely effective in improving clinical outcomes.”

It is likely that a second drug will be needed to reach target BP. As a second drug—“An ACE makes sense”.

ACE inhibitor: for patients with co-existing conditions, common in the elderly, ACE may be a first-line drug: diabetes, heart failure (combined with a diuretic), history of myocardial infarction.

Beta-blocker: first line for angina pectoris, heart failure, history of myocardial infarction.

Calcium blocker: first line for angina pectoris,

Choose a combination of drugs for which there is strong evidence of effectiveness with the type of problem found in the patient.:

See the following paper. RTJ

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“On The Basis Of Available Data, Diuretics Or Beta-Blockers Remain Appropriate For The Initial Treatment Of Uncomplicated Hypertension.”

2-3 INITIAL TREATMENT OF HYPERTENSION

This is one of a series of articles in NEJM which begin with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines when they exist. The article ends with the author’s clinical recommendations. (I abstracted a few quotes. RTJ)

“In patients over age 65, morbidity and mortality from cardiovascular disease are reduced when systolic blood pressure is lowered to a level below 160 mm Hg. Whether levels below 140 mm Hg provide additional protection is unclear.” “Optimal blood pressure targets remain to be determined, particularly for elderly patients.”¹

“Most combination therapies include small doses of a diuretic, which potentiate the effects of other drugs.” Combination therapy provides more rapid control of blood pressure than does monotherapy, and is therefore an initial treatment option for patients with stage 2 (160-179 and/or 90– 99), or stage 3 hypertension (180 and above and/or 110 and above).

“On the basis of available data, diuretics or beta-blockers remain appropriate for the initial treatment of uncomplicated hypertension.” “Alternative drugs are preferable for patients with certain coexisting medical conditions.” (*The author presents a table of indications on page 614.*)

“If no coexisting disease was detected, I would prescribe hydrochlorothiazide at a dose of 12.5 mg daily. If this dose did not control his blood pressure, I would increase it or add a second drug with complementary action—for example an ACE inhibitor. The latter option would prevent the adverse effects of higher doses on diuretics.”

NEJM February 13, 2002; 348: 610-616 “Clinical Practice”, commentary by Phyllis August, Weill Medical College of Cornell University, New York www.nejm.org

Comment:

1 Most authorities insist on reaching the goal of 140. Primary care clinicians may settle for a higher systolic BP. We deal with many elderly patients and try to treat them gently. I believe pushing drug therapy to achieve lower levels may result in more harm than benefit. I was glad to read this comment by Dr. August.

Lifestyle measures should be recommended for all patients with hypertension. The article reviews them. Unfortunately, compliance is poor. Patients would rather take a pill than diet and exercise.

I believe primary care clinicians should develop a firm drug protocol for treating long standing (ie, lifetime) illnesses. We should aim to provide the least expensive, least toxic drugs and drug doses, which are easiest to take, and more likely to lead to compliance.

We do not write a prescription for a diuretic”, a “beta-blocker” or an “ACE inhibitor”. We prescribe a specific drug, and dose. I suggest the following:

Choose generics. Over a lifetime they may save thousands. Avoid the “latest” and most advertised. Avoid starting therapy by giving samples of the newest drug and thus an impetus to continue it.

This suggestion is based on three generic drugs; a diuretic, a beta-blocker, and an ACE inhibitor in various combinations:

Uncomplicated hypertension (“White coat” hypertension ruled out):

Hydrochlorothiazide 12.5 mg; increase to hydrochlorothiazide 25 mg

Add atenolol 25 mg; increase to 50 mg

Add captopril 12.5 mg; increase to 25 mg

Systolic hypertension

Hydrochlorothiazide 12.5 mg; increase to hydrochlorothiazide 25 mg

Add atenolol 25 mg; increase to 50 mg

Add captopril 12.5 mg; increase to 25 mg

(Systolic hypertension occurs most often in the elderly. Go slow; don’t push dose.)

Complicated hypertension

Diabetes; Glucose intolerance

Captopril 12.5 mg; increase to 25 mg

Add hydrochlorothiazide 12.5 mg; increase to hydrochlorothiazide 25 mg

Add atenolol 25 mg; increase to 50 mg

History of myocardial infarction

Captopril 12.5 mg; increase to 25 mg

Plus atenolol 25 mg; increase to 50 mg

Add hydrochlorothiazide 12.5 mg; increase to hydrochlorothiazide 25 mg

Heart failure and left ventricular dysfunction.

Captopril 12.5 mg; increase to 25 mg

Plus atenolol 25 mg; increase to 50 mg

Plus hydrochlorothiazide 12.5 mg; increase to hydrochlorothiazide 25 mg).

Kidney disease (diabetic and non-diabetic)

Captopril 12.5 mg; increase to 25 mg

Add hydrochlorothiazide 12.5 mg; increase to hydrochlorothiazide 25 mg

Add atenolol 25 mg; increase to 50 mg

I believe we should avoid the more expensive (newer) drugs unless there is intolerance to the older drugs. The cost of the highest doses of the above 3-drug protocol can be reduced to about 30 cents daily. (*See previous abstract*) Shop around and use a pill cutter.

Individual clinicians may disagree and have a different protocol. But all need some sort of a protocol. RTJ

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Update On Melatonin—Is It Effective? The Cochrane Review Says It Is.

2-4 THE PREVENTION AND TREATMENT OF JET LAG.

Jet lag syndrome emerged with the rise of long air-travel. Symptoms include disturbed sleep, fatigue, loss of concentration, irritability during the new daytime, and difficulties in initiating and maintaining sleep during the new nighttime.

Jet lag is to be distinguished from travel fatigue. Travel fatigue can be distinguished from jet lag by comparing flights across time zones. For example, a long flight along the same meridian, as from England to South Africa, is not associated with jet lag. The same duration of flight across meridians as from England to Asia can cause jet lag in addition to travel fatigue.

(Simple practical advice to minimize travel fatigue is in a box on page 297)

Jet lag is due to a desynchronization between various body rhythms and environmental rhythms. The cycle of sleep is affected along with associated physical and mental functioning. The “body clock” controls secretion of melatonin by the pineal gland. Darkness turns it on, light turns it off. (*Melatonin is a “night-blooming” hormone.*) With rapid change of time zones, it takes several days for the external factors to shift the

phase of the clock from the just-left time zone to the new. Speeding up this adaptive shift can alleviate or prevent jet lag:

After a flight to the west, stay awake as long as it is daylight at the new destination and try to sleep when it gets dark.

After a flight to the east, try to be awake when it is morning in the new destination, but avoid bright light in the morning and be outdoors as much as possible in the afternoon.

(These measures will help readjust the body's own melatonin secretion to the new day-night time.)

Other helpful measures include: eating modestly at the times corresponding to one's usual mealtimes; taking comfortable exercise; seeing favorite sights at times of bright light.

Whether alcohol or caffeine affect adaptation is not clear. It probably depends on what the individual is used to. They seem more likely to hinder than help.

What about short-acting hypnotics? They induce sleep, but do not shift the circadian phase.

What about melatonin?

Taken at bedtime it shifts the phase and has hypnotic effect, but the importance of these two effects has not been established. A recent Cochrane Review found 10 randomized trials comparing melatonin with placebo in long distance travelers. Eight trials found a clear reduction in jet lag associated with melatonin. Five trials which reported global jet lag scores between zero [none] and 100 [extreme] found a mean score after placebo of 48, and after melatonin 25. One study reported that as many as one in two individuals using melatonin may benefit. It may be that not all symptoms of jet lag change at the same time and severity of symptoms may depend on the time of day they are assessed.

Adverse effects of melatonin are rarely reported. Two contraindications are in persons with epilepsy and those taking warfarin. It is freely sold in health food stores as a "dietary supplement". There are no standards of purity. Four of six melatonin products bought in the USA were found to contain unidentified impurities. "It seems advisable to buy it from a large reputable pharmacy chain and hope for the best." The internet offers a grey or black market.

The Cochrane Review concludes that 2 to 5 mg melatonin taken at bedtime at the new destination is effective, and may be worth repeating for the next two to four days together with the non-drug measures noted above.

BMJ February 8, 2003; 326: 296-97 Editorial, first author Andrew Herxheimer, UK Cochrane Centre, London
www.bmj.com/cgi/content/full/326/7384/296

Comment:

I abstracted this paper mainly to update on melatonin. Apparently it may be useful. I would remind patients that "dietary supplements" are not guaranteed as to purity, dose, or safety. Adverse effects are rarely published. "Take your chance if you wish."

I have wondered about the pineal. It is often calcified in older patients. It was used in the past as a classical radiological sign of cerebral hemispheric shift. Does the calcified gland maintain its secretory ability?

Lancet February 15, 2003; 361: 573-74 "Research Letter", first author T M MacDonald, Ninewells Medical School, Dundee, UK www.thelancet.com

Comment: Is this clinically important? I believe so, especially on the population level. Many millions are taking prophylactic aspirin. Many NSAIDs other than ibuprofen are available over the counter. . RTJ

"The Absence Of Infection Means That The Risk Of Cervical Cancer Is Negligible"

2-6 ADDING A TEST FOR HUMAN PAPILOMA VIRUS DNA TO CERVICAL-CANCER SCREENING

Virtually all squamous-cell cervical carcinomas contain one of eighteen types of human papilloma virus (HPV).¹ The relative risk of cervical cancer associated with high-risk types of HPV (*especially types 16 and 18*) is higher than the risk of lung cancer associated with smoking.

Continued presence of active HPV is necessary for maintenance of cervical cancer cell lines in vitro. Prospective epidemiological data demonstrate that *persistence* of infection is necessary for cervical carcinogenesis.

The discovery that *continued presence* of tumor-producing HPV is necessary for development of cervical cancer is revolutionizing our approaches to screening and prevention. An obvious correlary is that the absence of infection means that the risk of cervical cancer is negligible.

Testing for HPV DNA is now recommended for most women with equivocal findings on cervical cytology "Atypical Squamous Cells Of Undetermined Significance Low Grade Squamous Intraepithelial Lesion Triage; ASCUSLSIL" reported that a single HPV test identified virtually all women found to have high-grade precancerous lesions and was more effective than a single colposcopic examination or two Papanicolaou tests.

The editorialists suggest that the FDA will soon approve use of HPV DNA testing in conjunction with cytologic analysis for primary screening in women over age 30. The combined tests will allow the recommended interval between screenings be extended to 3 or more years.

The natural history of HPV infection must be taken into account. At present, most young women in the USA become infected within a few years after becoming sexually active. Multiple concurrent and sequential infections with different types of HPV are common. Most infections are transient and clinically insignificant, although they produce temporary cytologic changes. Fortunately, few HPV infected women actually become persistently infected (only about 10% remain infected at 5 years). Those with *persistent* infection have substantial risk (over 50%) of development of high-grade precancerous lesions or cervical cancer. Because most infections are destined to resolve spontaneously, it is important not to screen with excessive frequency. This will result in anxiety, unnecessary expenditures, and overtreatment with possible complications.

If HPV testing is incorporated in primary screening it will result in informing millions of women with normal Pap smears that they are at increased risk of cervical cancer. "The challenge is to develop clinical strategies that allow us to reap the benefits of HPV DNA testing without unduly alarming or over treating large numbers of

women.” Recent guidelines recommend that HPV testing be performed no more frequently than every 3 years in women over age 30. The problem of HPV positive women who have negative cytology remains.

“The greatest challenge will be assuring HPV DNA positive women that they should not be unduly alarmed or stigmatized while convincing them of the need for proper follow-up in order to identify those with persistent infection.”

NEJM February 6, 2003; 384: 489-90 “Perspective”, commentary by Thomas C Wright Jr. and Mark Schiffman, college of Physicians and Surgeons of Colombia University, New York.

Comment:

As usual, remarkable advances in screening bring remarkable problems. Properly implemented, this will bring reassurance to the women with suspicious Pap smears who are HPV negative.

1 See “Epidemiologic Classification Of Human Papilloma Virus Types Associated With Cervical Cancer.”

NEJM February 2, 2003; 348: 518-527

Combination therapy resulted in better control of symptoms and improved lung function

2-7 COMBINED SALMETEROL AND FLUTICASONE IN THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Inhaled long-acting beta-agonists improve lung function and health status in patients with symptomatic COPD. Inhaled corticosteroids reduce frequency of acute exacerbations and delay deterioration of health status.

This study asked—would the combination of the two be better than either alone?

Conclusion: The combination resulted in better control of symptoms and improved lung function.

STUDY

1. Multicenter, randomized, double-blind placebo-controlled parallel-group trial followed over 1400 out-patients with COPD. All had 1) baseline forced expiratory volume in one second (FEV_1) before bronchodilation between 25% and 70% of predicted and 2) an increase of less than 10% of predicted FEV_1 30 min after inhaling 400 mcg salmeterol, and 3) a prebronchodilator FEV_1 /forced vital capacity ratio of 70% or less. All had at least a 10 pack-years of smoking and at least one episode of an acute COPD exacerbation per year for the past 3 years, and at least one exacerbation in the year preceding the study which required treatment with oral corticosteroids, antibiotics, or both.
2. Randomized to:
 - 1) Salmeterol (*Serevent*) 50 mcg and fluticasone (*Flovent*) 500 mcg twice daily,
 - 2) Salmeterol alone
 3. Fluticasone alone, or
 - 2) Placebo.
3. Primary endpoint was change in FEV_1 .
4. Follow-up = 12 months

RESULTS

1. All 3 active treatments improved lung function, symptoms, and health status. And reduced use of rescue medication and frequency of exacerbations.
- 2) Combination treatment improved FEV₁ significantly more than placebo or the other two drugs used alone compared with placebo:

Combined	+ 133 mL:
Salmeterol alone	+ 73 mL
Fluticasone alone	+ 95 mL

(Benefits were evident at 2 weeks and were sustained throughout treatment.)
3. The differences in FEV₁ between treatment groups was unaffected by whether the participant continued to smoke. (Indeed, only 6% to 7% of participants changed their smoking habits.)
4. Exacerbations fell by 25% in the combination group vs 20% and 19% in the other treatment groups, as compared with placebo. And requirements for oral corticosteroids fell by 39%, 29% and 34% compared with placebo.
5. Treatment effect was greatest in patients with more severe disease.
6. Combination treatment produced a clinically significant improvement in health status (by a health status score) and the greatest reduction in daily symptoms.
7. All treatments were well tolerated, with no difference in frequency of adverse events, bruising, or clinically significant fall in serum cortisol concentration.

DISCUSSION

1. Combination treatment produced clinical benefits across a range of endpoints.
2. Combination treatment produced a significantly greater improvement in FEV₁.

CONCLUSION

Combined inhaled long-acting beta agonist/corticosteroid produced better control of symptoms and lung function with no greater risk of adverse effects than the use of either component alone.

“This combination treatment should be considered for patients with COPD.”

Lancet February 8, 2003; 361: 449-56 Original investigation by the TRISTAN Study Group (Trial of Inhaled STeroids And long-acting beta-agonists) first author Peter Calverley, University Hospital Aintree, Liverpool, UK www.thelancet.com

An editorial in this issue of Lancet (pp 444-45) comments:

The patients evaluated in the study were selected for their lack of reversibility. (less than 10% improvement in FEV₁ by beta agonist). This was an attempt to exclude any subject who might have had asthma, despite recent studies which suggest that most patients with COPD have at least a limited degree of reversibility. The study therefore specifically evaluated the group least likely to show improvement.

Comment:

This combined treatment may not be easily applied to patients in primary care. Of 1465 patients enrolled, many withdrew. Albeit fewer in the combined group.

It is astounding that so few stopped smoking.

The study lasted for only one year. I would feel more secure if anti-bone-resorptive therapy were given to these patients on long-term corticosteroids, despite the lesser risk of osteoporosis related to inhaled corticosteroids. Long-term regular doses of *Serevent* should be accompanied by inhaled corticosteroid. See following. RTJ

GlaxoSmithKline has recently issued a "Safety Alert" about *Serevent*. The Salmeterol Multi-center Asthma Research Trial, begun in 1996, is a 28-week safety study comparing *Serevent* with placebo in treatment of asthma. End points included asthma-related life-threatening experiences, including death. Subjects received a 42 mcg inhalation twice daily.

At end of 2002, over 25 000 patients had been treated. There was a statistically significant *increased* risk of life-threatening events and deaths in African Americans (17% of subjects) who were *not* taking inhaled corticosteroids concomitantly. In Caucasians, no differences were apparent. However, less than 1% of African Americans experienced these events during the 28 weeks.

In subjects taking inhaled corticosteroids along with the *Serevent*, there was no difference in outcomes. (Ie, corticosteroids seemed to blunt the adverse effect.)

Patients who require more than-as-needed short-acting beta-agonists should take regular and adequate doses of inhaled corticosteroids.

A Protective Effect Of Light-To-Moderate Alcohol Consumption On Ischemic Stroke; Not On Hemorrhagic Stroke.

2-8 ALCOHOL CONSUMPTION AND RISK OF STROKE: A Meta-analysis

Observational studies suggest that heavy alcohol consumption may increase risk of stroke. Moderate consumption may decrease risk.

This study examined the association between alcohol consumption and relative risks of stroke to further clarify the association.

Conclusion: Light-to-moderate consumption may be protective. Heavy consumption increases risk.

STUDY

1. Systematic search found 35 relevant observational studies.
2. Used pooled data from individual studies to determine risk of stroke according to the amount of alcohol consumed. Abstinence was used as the reference group.

RESULTS

1. Consumption of more than 60 g alcohol per day was associated with increased risk of total stroke, ischemic stroke, and hemorrhagic stroke. (Relative risks = 1.6, 1.4, and 2.2.)
2. Consumption of less than 12 g per day was associated with reduced risk of total stroke and

ischemic stroke (RR = 0.83 and 0.80)

3. Consumption of 12 to 24 g per day was associated with a reduced risk of ischemic stroke (RR = 0.7.2)

4. There was a non-linear association between quantity of alcohol consumed and risk of ischemic stroke.

A “J shaped” curve indicated that, compared with abstinence, light to moderate consumption of alcohol reduced risk.

5. There was, however, a linear relationship between alcohol consumption and hemorrhagic stroke.

(Ie, no protective effect at any level of consumption.)

DISCUSSION

1. This meta-analysis found a protective effect of light-to-moderate alcohol consumption on ischemic stroke; not on hemorrhagic stroke.

2. The authors suggest several mechanisms for the protective effect on ischemic stroke: increase in HDL-cholesterol; increased fibrinolytic activity; decreased platelet activity. (Ie, an anticoagulant effect.)

3. “Any advice regarding the consumption of alcohol should be tailored to the individual patient’s risks and potential benefits.”

CONCLUSION

Heavy alcohol consumption increases risk of stroke. Light-to-moderate consumption protects against ischemic stroke, but not against hemorrhagic stroke.

JAMA February 5 2003; 289: 579-88 Original investigation, first author Kristi Reynolds, Tulane University School of Public Health and Tropical Medicine, New Orleans. LA

Comment:

The protective effect of alcohol on cardiovascular disease has been reported for several decades.

Over the past 4 years, *Practical Pointers* has abstracted 9 studies all of which reported a protective effect on various outcomes: myocardial infarction, hypertension, diabetes, stroke, coronary heart disease, dementia, insulin sensitivity and glucose metabolism, and triglyceride concentrations. Although publication bias may account for some of the benefits reported, the studies are remarkably consistent, so much so that some authorities consider abstinence a risk factor.

I believe the protective association is established. Primary care clinicians have an opportunity and responsibility to apply this knowledge to individual patients. If alcohol were a prescription drug, use would be universal. RTJ

Immediate Benefits From A Go-Low Go-Slow Dose In Euvolemic Patients

2-9 EFFECTS OF INITIATING CARVEDILOL IN PATIENTS WITH SEVERE CHRONIC HEART FAILURE

Beta-blockers prolong life and reduce risk of disease progression in patients with chronic heart failure. (HF). They remain underused despite their established utility. This may be because of concerns that initiation of

treatment produces few immediate benefits while incurring important risks. There are also concerns that treatment is difficult and requires special expertise, and that patients starting the drugs may experience hypotension, retention of sodium, and possibly worsening HF during the first few weeks of therapy. Many physicians assume that the benefits of therapy are delayed, so that a favorable effect on symptoms, hospitalizations, and death may not become apparent for months.

Studies have suggested that initiation of therapy is well tolerated in patients with mild HF, but is associated with an early increase in risk of worsening HF leading to withdrawal of the drugs in patients with severe HF.

This study evaluated the *early* effects of the beta-blocker carvedilol (*Coreg*) in patients with *severe* HF.

Conclusion: In clinically euvolemic individuals with severe HF, the benefit of beta-blocker therapy was similar to that seen during long-term therapy.

STUDY

1. Multicenter, randomized, double-blind, placebo-controlled trial followed over 2200 patients. All had symptoms of HF at rest or with minimal exertion. All were clinically euvolemic at baseline. Mean ejection fraction was less than 25%.
2. All were treated with a diuretic, dose adjusted to minimize the degree of volume retention. Most received an ACE inhibitor or an angiotensin II blocker. Other medications continued as usual.
3. Randomized to: 1) carvedilol 3.125 mg twice daily, or 2) placebo. Dose gradually increased (6.25 mg, 12.5 mg, and then 25) at 2-week intervals to a target dose of 25 mg twice daily. The added dose was administered only if the drugs were being well tolerated.
4. A subset of very high risk patients with left ventricular ejection fractions less than 15% and more acute symptoms, including current hospitalization, was randomized separately.
5. Followed for outcomes and withdrawals during the first 8 weeks.

RESULTS

- | | | |
|---------------------------------------|-----------------------|--------------------|
| 1. Outcomes at 8 weeks | Carvedilol (N = 1133) | Placebo (N = 1156) |
| Death | 19 | 25 |
| Death or hospitalization | 134 | 153 |
| Death, hospitalization, or withdrawal | 162 | 188 (NNT = 50) |
| 2. Outcomes for high risk patients | (N = 308) | (N = 316) |
| Death | 3 | 15 |
| Death or hospitalization | 44 | 63 |
| Death, hospitalization, or withdrawal | 51 | 76 (NNT = 12) |
3. “High risk” patients (with recent or recurrent decompensation or with a very depressed left ventricular ejection fraction) received even more benefits than average risk patients.
 4. At 8 weeks, 59% of the carvedilol patients were receiving 25 mg twice daily.
 5. Significant differences in outcomes began to appear as early as 14 to 21 days.

6. There was no difference between placebo and carvedilol in the number of patients withdrawn due to worsening HF. (5.1% vs 4.4%)
7. Dizziness, hypotension, edema, and bradycardia were more common in the carvedilol group. The investigators did not consider these serious adverse effects.

DISCUSSION

1. During both initiation and up-titration, patients treated with carvedilol had no increase in the risk of worsening HF, pulmonary edema, cardiogenic shock, or other serious adverse cardiovascular events, including death.
2. Other adverse effects (eg, dizziness and hypotension) were mild ¹ and infrequent, and not considered serious.
3. This study challenges the belief that the benefits of beta-blockade in patients with HF are delayed.
The ability of carvedilol to produce beneficial effects early during the course of treatment was particularly striking among patients with recent decompensation and very low ejection fractions.
4. Benefits were evident at about day 21, a time when patients were generally receiving only 6.25 mg twice daily.
5. Note that the investigators were highly experienced in treatment of HF. Patients were followed closely.
They were made clinically euvolemic at onset, and every effort was made to maintain euvolemia.

CONCLUSION

Benefits of beta-blocker therapy with carvedilol were evident within a few weeks in patients with advanced HF who were euvolemic. Benefits were similar to those obtained by long-term therapy.

Initiation of treatment was well tolerated.

JAMA February 12, 2003; 289: 712-188 Original investigation, first author Henry Krum, Monish University, Melbourne, Australia. www.jama.com

Comment:

The study was terminated early because of perceived benefits.

It should be emphasized that patients were made euvolemic prior to onset therapy and kept euvolemic. They were followed closely with adjustments based on tolerance.

I believe primary care clinicians should prescribe low-dose beta-blockers more readily to select patients. It may be prudent not to push to the maximum dose, but to stop at a lower dose (eg, 6.25 mg twice daily). RTJ

1 It amuses me at times when authors state adverse effects are “mild”. This opinion should come from the patients.

Use Lower Doses

2-10 ASSOCIATION OF SERUM DIGOXIN CONCENTRATION AND OUTCOMES IN PATIENTS WITH HEART FAILURE.

The Digitalis Investigation Group (**DIG**) trial¹ reported that digoxin provides no overall mortality benefit in patients with heart failure (**HF**), and only a modest reduction in hospitalizations due to worsening HF.

Since this report, concerns have been raised regarding the relative efficacy of serum digoxin concentrations greater than 1.0 ng/mL. Higher concentrations have not shown a beneficial effect on neurohormonal function², hemodynamics, or exercise tolerance. This led to the guideline recommendations that larger doses of digoxin may not be more effective than small doses in the treatment of HF.

This study assessed variations in serum digoxin concentrations and their association with mortality and hospitalization in patients with HF.

Conclusion: Higher serum concentrations were associated with increased mortality. Optimum level may be in the range of 0.5 to 0.8 ng/mL.

STUDY

1. The DIG trial in 1997 randomized over 3700 men with HF to 1) digoxin or 2) placebo. All subjects had HF with a left ventricular ejection fraction under 45%. All were in sinus rhythm.
2. This study, a post hoc analysis of the DIG trial, divided patients who received digoxin into 3 groups according to their serum digoxin concentrations at one month: 0.5 to 0.8 ng/mL; 0.9 to 1.1 ng/mL; and 1.2 ng/mL and above.
3. Main outcome measure = all cause mortality at a mean of 37 months follow-up.

RESULTS

1. Higher serum concentrations were associated with increased crude all-cause mortality during follow-up:

0.5 to 0.8 ng/ml	30%
0.9 to 1.1 ng/mL	39%
1.2 ng/mL and above	48%
2. Patients with concentrations of 0.5 to 0.8 ng/ml had a 6% lower mortality than patients receiving placebo.
NNT(3 years to benefit one patient) = 16.
3. Patients with higher concentrations had a 3% to 12% higher mortality than those receiving placebo.
4. The association persisted after multivariable adjustments.

DISCUSSION

1. Effectiveness of digoxin varied according to serum concentrations. Higher concentrations were associated with higher mortality.
2. The previously accepted concentrations of 1.2 ng/mL and higher maybe harmful, and the

currently recommended therapeutic concentrations of approximately 1.0 ng/mL may not provide any clinical benefit compared with placebo.

3. A concentration of 0.5 to 0.8 ng/mL likely constitutes the optimal therapeutic range.
4. Higher concentrations may reflect inotropic-associated increase in oxygen consumption and arrhythmias.

The association between serum levels and patient outcomes may reflect the dissociated neurohormonal and inotropic effects of digoxin observed at different concentrations. Neurohormonal modulation is believed to contribute to digoxin's symptomatic benefits among patients with stable HF who are in sinus rhythm. In contrast, digoxin-associated harms are believed to reflect inotropic-associated increases in myocardial oxygen consumption and arrhythmogenesis as serum concentrations rise to a higher level. The findings are consistent with the hypothesis that, at lower serum concentrations, digoxin provides a neurohumoral benefit without increasing inotropic-associated risk. As serum concentrations increase, the inotropic action of digoxin begins to offset the therapeutic benefits provided by neurohumoral modulation and may account for the increased risk of higher concentrations.

5. Beta-blockers were not a part of the study, making it unclear whether the outcomes would be altered by beta-blocker therapy.
6. The data provide consideration of lower target serum concentrations in patients with stable heart failure and sinus rhythm.

CONCLUSION

Higher serum concentrations of digoxin were associated with increased mortality in patients with HF who were in normal sinus rhythm. The most effective concentration may be 0.5 to 0.8 ng/mL

JAMA February 19, 2003; 289: 871-78 Original investigation, first author Saif S Rathore, Yale University School of Medicine, New Haven, Conn. www.jama.com

1 "The Effect of Digoxin on Mortality and Morbidity in Patient with Heart Failure" NEJM 1997; 336: 525-33

2 *Goodman and Gilman* textbook of pharmacology refreshed my memory about the effects of digoxin on the sympathetic nervous system:

In HF, sympathetic nervous system function and production of norepinephrine are enhanced as a mechanism which compensates for the reduced cardiac output and reduced peripheral blood flow. (I.e., an effort to sustain BP and cardiac output.) This eventually becomes counterproductive as cardiac function worsens.

One effect of digoxin is to reduce activity of the sympathetic nervous system. (Akin to the action of beta-blockers, albeit not by the same pharmacologic mechanism.) This central nervous system action of digoxin is one way in which it leads to a reduced heart rate and increased peripheral blood flow.

This study pointed out that higher doses do not enhance this activity any more than low-doses. RTJ

“May Have A Substantial Impact On The Most Common Mechanism Of Death”

2-11 CARDIAC RESYNCHRONIZATION AND DEATH FROM PROGRESSIVE HEART FAILURE

Progressive heart failure (HF) is the most common mechanism of death among patients with advanced HF. A gradual loss of ventricular function leads to inadequate systemic perfusion.

Cardiac resynchronization, a pacemaker-based therapy for HF, enhances cardiac performance and quality of life.

Abnormal electrical activation of the ventricles (ventricular dyssynchrony) is common in advanced HF. It is manifest in the ECG as prolongation of the QRS interval, often in the pattern of left bundle branch block. Prolonged QRS has been associated with diminished cardiac function and increased mortality.

Recently, cardiac pacemakers have been modified to correct ventricular dyssynchrony. The new pacemakers use a left ventricular lead that ensures stimulation of the left ventricle at, or near, the time of right ventricular depolarization. This synchronization enhances cardiac function and reduces myocardial oxygen consumption. It improves exercise capacity, functional class, and quality of life.

This study asks: What is its effect of cardiac resynchronization on mortality?

Conclusion: Mortality from progressive HF was reduced from 3.5% to 1.7% over 6 months among patients with advanced HF.

STUDY

1. Systematic search selected 4 randomized trials of over 1600 patients. (Ages 63 to 66) Mean left ventricular ejection fraction ranged from 21% to 23% (functional class III and IV). QRS duration was prolonged in all, the majority due to left bundle branch block. All had the new pacemakers installed.
2. The great majority of patients were receiving ACE inhibitors. Some were receiving beta-blockers.
3. Randomized to: 1) Resynchronization on, or 2) Resynchronization off.
4. Follow-up = 3 to 6 months.

RESULTS

- | 1. Outcomes at 3 to 6 months: | Resynchronization (N = 809) | No resynchronization (N = 835) |
|-------------------------------|-----------------------------|--------------------------------|
| Death from progressive HF | 14 (1.7%) | 29 (3.5%) |
| Non-HF deaths | 26 | 23 |
| All-cause deaths | 40 | 52 |
2. Absolute reduction in death from progressive HF = 1.8%; NNT(6 months to benefit one patient) = 55.
 3. Hospitalizations for HF were also reduced (13% vs 17%). Absolute reduction = 4%; NNT = 25.

DISCUSSION

1. This study extends the benefits of resynchronization from the previously noted improvements in exercise capacity, functional class, and quality of life, to a benefit in length-of-life. “This finding is important because approximately one half of all deaths among patients with severe heart failure results from progressive cardiac dysfunction.”

2. The characteristics of patients in these trials are typical of about 10% of heart failure patients. The number of such individuals in the population may approximate 500 000. Economic benefits may be substantial.
3. The benefits of resynchronization are biologically plausible, given the improvement in cardiac function, and improvement in exercise capacity, functional class, and quality-of-life.
4. Long-term beta-blocker therapy is associated with a similar reduction in death from worsening HF.
“Cardiac resynchronization may allow enhancement of beta-blocker therapy in patients with heart failure by prevention of bradycardia.”
5. “We found a 51% relative reduction in death from progressive heart failure among 1634 patients randomized to cardiac resynchronization vs control” “We found an encouraging . . . 23% relative reduction in all-cause mortality among patients treated with cardiac resynchronization vs controls.”¹
6. The relatively short observation period (3 to 6 months) does not permit assessment of long-term benefits. However, uncontrolled evidence showed that resynchronization was well tolerated after 2 years.

CONCLUSION

Cardiac resynchronization reduced mortality from progressive heart failure in patients with symptomatic left ventricular dysfunction and left bundle branch block.

This may have a substantial impact on the most common mechanism of death among patients with advanced heart failure.

JAMA February 12, 2003; 289: 730-40 Meta-analysis, first author David J Bradley, John Hopkins Hospital, Baltimore MD. www.jama.com

Comment:

This study may influence primary care clinicians to watch for increasing symptoms of HF in patients with left bundle branch block, and to refer them more readily and earlier to cardiologist consultants.

1 Editors still seem unable to get away from reporting the non-clinically-relevant “relative” benefits. And seem reluctant to report the clinically relevant “absolute” benefits. (Ie, the NNT) RTJ

A Valid Risk Marker. But Is It Applicable To Primary Care?

2-12 PANEL INDORSES LIMITED ROLE FOR CRP TESTS

How should physicians estimate future risk cardiovascular disease (CVD)? The Framingham Heart Study Prediction Score has been used for years. *[The importance of the estimation lies in the opportunity to modify risk by lifestyle measures and prophylactic drug therapy (eg, aspirin; statin drugs).]*

C-reactive protein (CRP) has received much publicity recently as an independent risk marker. CRP has emerged as the leading inflammatory marker for CVD.

An expert panel of the American Heart Association and the Centers for Disease Control and Prevention (CDC) has issued recommendations about high-sensitivity CRP (**hs-CRP**). The panel felt there is compelling

evidence that CRP does indeed have predictive ability. The questions are: Does the test add anything to the list of risk markers now available? How should it be used?

A number of unresolved issues prevent the medical community from embracing CRP testing: lack of standardization; inconsistent epidemiological findings; and lack of evidence that testing will add anything to established risk factors.

The panel suggests that CRP has its greatest utility in people deemed at intermediate risk of CVD. (intermediate risk = 10% to 20% risk of developing CVD in the next 10 years as calculated from the Framingham risk score.

It should be used in metabolically stable patients. It should not be used in patients with inflammatory disease or infections. (False positive screening result.)

Patients with a hs-CRP level below 1.0 mg/L have low risk. 1.0 to 3.0 are at intermediate risk; over 3.0 at high risk. The high risk patients have about a two-fold risk for CVD.

Physicians should assess traditional risk factors and calculate the absolute Framingham risk score. <http://hin.nhlbi.nih.gov/atp/iii/calculator.asp?usertype=prof> before testing with CRP. It should not be used routinely, or as an alternative to traditional risk factor assessment. It is not known if an elevated CRP by itself needs treatment. An elevated level might motivate patients to greater compliance with life style measures and prophylactic drug therapy.

The blood test costs about \$15 to \$20.

Much uncertainty remains.

JAMA February 26, 2003; 289: 973-74 "Medical News and Perspectives" commentary by Mike Mitka, JAMA staff. www.jama.com

Comment:

I believe primary care clinician's chief problem and opportunity is control of established risk factors. Until we do, application of another risk factor will add little clinical value.

It would be interesting to speculate that CRP might replace some of the other risk factors, thus simplifying prediction risk scores. RTJ

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