

PRACTICAL POINTERS
FOR
PRIMARY CARE
ABSTRACTED MONTHLY FROM THE JOURNALS
JULY 2001

ADD TEN YEARS TO YOUR LIFE

BOLUS FIBRINOLYTIC THERAPY

ALBUMINURIA AND RISK OF CARDIOVASCULAR EVENTS

ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND PROGRESSION OF RENAL DISEASE

PATIENT-INITIATED TREATMENT OF RECURRENT URINARY TRACT INFECTIONS

RISK OF HRT ON CARDIOVASCULAR DISEASE IN TYPE 2 DIABETES.

POSTMENOPAUSAL HORMONE USE AND PREVENTION OF CORONARY EVENTS

RISK OF RECURRENT CORONARY EVENTS IN RELATION TO USE OF HRT

ANALGESIC USE AND RENAL FUNCTION IN MEN

PHYSICAL ACTIVITY AND COGNITIVE DECLINE IN ELDERLY WOMEN.

**ACUTE EFFECTS OF PASSIVE SMOKING ON THE CORONARY CIRCULATION MANAGEMENT D-DIMER TESTING FOR
SUSPECTED DEEP VENOUS THROMBOSIS**

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THREE MONTHS VS ONE YEAR OF ORAL COAGULATION AFTER TOTAL HIP REPLACEMENT

THREE MONTHS VERSUS ONE YEAR OF ORAL ANTICOAGULANT THERAPY FOR DVT

PANIC DISORDER

SINGLE-DOSE DOXYCYCLINE FOR THE PREVENTION OF LYME DISEASE

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HIGHLIGHTS JULY 2001

7-1 TEN YEARS OF LIFE

Life-style choices regarding diet, exercise, smoking, body weight, and hormone replacement singly and in combination appeared to lengthen life-expectancy by many years.

Practical point: Primary care clinicians should adopt these lifestyles themselves. Then they can encourage patients to do likewise. Publication of this study might motivate some patients.

7-2 BOLUS FIBRINOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION

Given the ease of administration and the similar outcomes compared with recombinant tPA, it is likely that a key component of reperfusion will include a bolus fibrinolytic. The simple bolus administration should shorten the time between onset of symptoms and treatment (onset-to-needle time). It should facilitate pre-hospital fibrinolysis and improve prognosis.

Practical point: Primary care clinicians who do not have immediate access to emergency department consultations should be able to administer the newer bolus fibrinolytics in the office.

7-3 ALBUMINURIA AND RISK OF CARDIOVASCULAR EVENTS, DEATH, AND HEART FAILURE IN DIABETIC AND NON-DIABETIC INDIVIDUALS.

Any degree of albuminuria is a robust, independent risk factor for future cardiovascular events in individuals without DM who have increased risk factors for CVD, as well as those with DM. The risk increases as the albumin/creatinine ratio increases, starting well below the cutoff for microalbuminuria.

Practical point: Primary care clinicians should screen for albuminuria (both dipstick positive and below) in diabetic patients and high risk patients without diabetes. It is an inexpensive and rewarding prognostic indicator which calls for early intervention.

7-4 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND PROGRESSION OF NON-DIABETIC RENAL DISEASE: Meta-analysis of Patient-Level Data

Antihypertension regimens which include ACE inhibitors are more beneficial in slowing the progression of non-diabetic renal disease than regimens that do not contain ACE.

Practical point: Chronic renal insufficiency is under-diagnosed and under-treated. Opportunities for prevention are lost. The presence of proteinuria in chronic renal disease is a strong indication for treatment with ACE. ACE inhibitors should be the antihypertensive agents of first choice in nondiabetic renal disease as well as in diabetic renal disease.

7-5 PATIENT-INITIATED TREATMENT OF UNCOMPLICATED RECURRENT URINARY TRACT INFECTIONS IN YOUNG WOMEN

Motivated and adherent young women can accurately self-diagnose and self-treat recurrent UTIs.

Practical point: Primary care clinicians should make this option available to select patients.

7-6 THE EFFECT OF HORMONE REPLACEMENT THERAPY ON CARDIOVASCULAR RISK FACTORS IN TYPE 2 DIABETES.

There is compelling evidence that HRT exerts beneficial effects on a number of cardiovascular risk factors in non-diabetic women. This study demonstrated its beneficial effect on women with type 2 diabetes.

Practical point: This may reassure those of us who believe HRT ultimately improves risk of CHD. All patients with diabetes must be especially vigilant in reducing risk factors for cardiovascular disease. This includes routine use of low-dose aspirin. Use of aspirin during the first few months of HRT use, when there is increased risk of cardiovascular events, may be a reasonable strategy for non-diabetic patients as well as diabetic patients.

7-7 POSTMENOPAUSAL HORMONE USE AND SECONDARY PREVENTION OF CORONARY EVENTS IN THE NURSES' HEALTH STUDY

The risk of recurrent major coronary events seems to be increased among short-term hormone users with previous coronary disease. With continued use beyond 1 year, risk decreases to a level below the risk in non-users.

Practical point:

I believe primary care clinicians can reasonably give the following advice:

1. HRT should be started early in the premenopausal or immediate postmenopausal time period when women, because of their younger age, will have less risk of coronary events.
2. HRT might be avoided if possible even at an early age in women at high risk (eg, smokers, those with lipid disorders, hypertension).
3. Women with troublesome menopausal symptoms might be started on low dose estrogen (eg, 0.3 mg *Premarin*) until the danger period of 1 year is passed. Low-dose aspirin prophylaxis should be given.

7-8 RISK OF RECURRENT CORONARY EVENTS IN RELATION TO USE AND RECENT INITIATION OF POSTMENOPAUSAL HORMONE THERAPY

After a first myocardial infarction, use of HRT suggested a transient rise in risk of recurrent coronary events in the first 60 days. Thereafter, use of HRT (compared with non-use) suggested a reduction in risk (ie, a benefit).

Practical point: I do not believe HERS and other studies should deter primary care clinicians from prescribing HRT for most patients who opt to take them. These results reinforce the preceding study. Starting HRT at or before the menopause when women are younger, and avoiding use by those with many CVD risk factors would be prudent.

With due care, and concomitant use of aspirin for its anti-platelet effect, any increased risk in the first months would be avoided and thereafter a reduction of cardiovascular events would be likely as women grow older.

7-9 ANALGESIC USE AND RENAL FUNCTION IN MEN

This provides reassurance that there is not a strong relationship between chronic (up to 4 years) moderate use of acetaminophen, aspirin, and other NSAIDs and development of renal disease in persons with normal renal function.

This does *not* provide reassurance among those with initial renal dysfunction. NSAIDs in these patients may lead to further kidney dysfunction.

Primary care clinicians must remember that NSAIDs can have a deleterious effect on patients with heart failure and hypertension through their pharmacological effect on the kidney.

7-10 A PROSPECTIVE STUDY OF PHYSICAL ACTIVITY AND COGNITIVE DECLINE IN ELDERLY WOMEN.

Elderly women with higher levels of baseline physical activity were less likely to develop cognitive decline over the next 6 to 8 years.

Practical point: Another point for clinicians to encourage fitness over a lifetime.

7-11 ACUTE EFFECTS OF PASSIVE SMOKING ON THE CORONARY CIRCULATION IN HEALTHY YOUNG ADULTS.

Passive smoking substantially reduced coronary blood flow reserve in healthy non-smokers. Passive smoking may cause endothelial dysfunction in the coronary circulation in non-smokers.

This should convince the diehards who still maintain that harms of passive smoking are not proven. It strengthens the resolve of those who oppose smoking in public places

7-12 MANAGEMENT OF SUSPECTED DEEP VENOUS THROMBOSIS IN OUTPATIENTS USING CLINICAL ASSESSMENT AND D-DIMER TESTING

The combination of a low pretest probability of DVT and a negative D-dimer test rules out DVT.

Practical point: Primary care clinicians may use a D-dimer test to help *rule out* DVT in select low probability patients. D-dimer is not useful in *ruling in* DVT. It is not useful in patients with moderate or high probability of DVT.

7-13 SUBCLINICAL HYPOTHYROIDISM

Routine screening, especially of older women, has been advocated, although not endorsed unanimously. The benefits of subsequent therapy have not been established in prospective trials. However, a decision and cost-effectiveness model calculated that screening women over age 35 every 5 years would be beneficial. Half the benefit would be from prevention of subsequent overt hypothyroidism, 30 percent for improved symptoms, and a smaller benefit from improvement in serum lipids.

Prevention of progression to overt hypothyroidism has been found to be about 4% per year in women with both an elevated TSH and antithyroid antibodies. (38 times that of women with normal values.) The NNT to prevent one patient from developing overt hypothyroidism = 4 to 14.

Practical point: Primary care clinicians must decide on long-term thyroxine supplementation or continued observation. I believe cautious supplementation is the best choice.

7-14 CAM RESEARCH ATTEMPTS TO SEPARATE WHEAT FROM CHAFF

The National Center for Complementary and Alternative Medicine (part of the NIH) is attempting to develop a more thorough understanding of how herbs react in the body.

Several multicenter, randomized trials are being conducted. Primary care clinicians should watch for developments.

7-15 HERBAL MEDICINES AND PERIOPERATIVE CARE.

Many potential adverse effects may occur in patients taking herbal medicines before surgery.

During the perioperative evaluation, physicians should explicitly elicit and document a history of herbal medicine use.

Practical point: Primary care clinicians should be familiar with potential adverse effects of complementary-alternative medicines in order to recognize, prevent, and treat serious problems associated with their use.

7-16 EXTENDED-DURATION PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM AFTER TOTAL HIP OR KNEE REPLACEMENT

Among patients undergoing elective hip and knee replacement, outpatient LMW heparin continued for 4 to 6 weeks after discharge reduced the frequency of DVT.

Practical point: For the many patients for whom extended heparin or warfarin is not feasible, aspirin should be considered an option.

7-17 THREE MONTHS VERSUS ONE YEAR OF ORAL ANTICOAGULANT THERAPY FOR IDIOPATHIC DEEP VENOUS THROMBOSIS.

In patients with acute idiopathic DVT, continuing anticoagulation for 1 year reduced recurrence during that year. However, after discontinuing anticoagulation, thrombosis recurred at a rate similar to the rate in those who discontinued after 3 months.

Practical point: Primary care clinicians face the decision – continue or discontinue anticoagulation? I believe the answer depends on the severity of the DVT, the preference of the patient, and the local availability of logistic support for anticoagulation. If discontinued, recurrence is likely. We should search for underlying thrombogenic factors in these patients. If the decision is made not to continue warfarin, these patients should be placed on continuous aspirin.

7-18 A 28-YEAR OLD WITH PANIC DISORDER

A clinical review article defining panic attack and panic disorder. Comments on diagnosis and treatment. "The cause is not known, but treatment is almost always successful."

7-19 PROPHYLAXIS WITH SINGLE-DOSE DOXYCYCLINE FOR THE PREVENTION OF LYME DISEASE AFTER AN *IXODES SCAPULARIS* TICK BITE

A single dose of doxycycline given within 3 days of a recognized tick bite prevented development of Lyme disease.

Who should receive prophylactic doxycycline?

Persons bitten by ticks in endemic areas.

The tick is at least partially engorged.

The tick is a nymphal deer tick.

Practical point: This applies to only a few primary care clinicians. The application is important to them and their patients.

The remarkable benefits of a healthy lifestyle.

7-1 TEN YEARS OF LIFE: *Is It a Matter of Choice?*

"An underlying goal of therapeutic and preventive medicine is to increase the number of productive and satisfying years of life."

Effective implementation of life-style behaviors commonly advocated in preventive medicine increases life expectancy.

Relative risks are an appropriate means of reporting results for research purposes. However, the authors suggest that the general public and probably non-epidemiologic medical practitioners may find results expressed as predicted extra years of life, or delay of age at onset of a specific disease, equally, if not more, useful.

This study was designed to test the hypothesis that choices regarding diet, exercise, and smoking influence life expectancy. The authors expressed it in years of life gained or lost.

Conclusion: Individuals who maintained healthy life-styles lived considerably longer.

STUDY

1. Enrolled a cohort of over 34 000 California Seventh-Day Adventists (75% of those eligible) and followed up from 1976 to 1988.
2. Extensive lifestyle questionnaire determined medical history, diet, physical activity, and a few psychosocial variables.
3. Ascertained mortality of all subjects.

RESULTS

1. Percentage of the cohort who adopted various lifestyles:

Vegetarian	30%
Eat nuts at least 5 times weekly ¹	23%
Exercise vigorously for 15 minutes at least 3 times weekly	40%
Ever use of hormone therapy (HRT by women)	53%
Smokers (current)	Nil
Body mass index (mean)	25

2. Except for abstinence from smoking, more than half Adventists did not adhere to these lifestyle variables; fewer than half complied. Compared with adherers, those that did not comply lost more than 4 years of life.
3. Each variable (eg, vegetarian vs non-vegetarian; high exercise vs low; high nut consumption vs low; low BMI vs high; never smoker vs past smoker; HRT ever vs HRT never) resulted in an approximate 1.5 to 2.5 years gain in life expectancy, compared with the corresponding high risk variables.

DISCUSSION

1. California Adventists have higher life expectancy at age 30 than other white Californians. (Females + 7 years; males + 4 years; expected ages at death — men = 83, women = 86). This is the highest life expectancy of any formally described population.
2. Behavioral choices extended the expected age at death by several years, even as much as a decade.
2. "Evidence of the benefits associated with these behaviors can be used to motivate change."
3. "Adventist women can anticipate fewer years of widowhood, assuming their husbands are also Adventist."
4. Substantial gains in life expectancy would be worthwhile only if they are accompanied by a longer period of good-quality life. It was previously shown that vegetarian Adventists took less medication, and had fewer hospital stays, surgical procedures and X-ray examinations. They also had reduced prevalence of several chronic diseases.
5. The vegetarian diet provides greater intakes of unsaturated fat; lower saturated fat; higher fiber, and antioxidant vitamins. Those that consume more nuts have been shown to have lower rates of coronary events. ¹

CONCLUSION

Life-style choices regarding diet, exercise, smoking, body weight, and hormone replacement singly and in combination appeared to be related to lengthened life-expectancy by many years.

Archives Int Med July 9, 2001; 1671: 1645-52 Original investigation by Gary E Fraser and David J Shavlik, Loma Linda University, California. www.archinternmed.com

1 The Loma Linda group has been enthusiastic about the health benefits of nuts. Nuts have now entered the food pyramid
 Comment:

These results are not surprising. The quantitation might influence some to adopt a more healthy lifestyle.

No mention of alcohol. I presume the group used no alcohol. It would be interesting to determine if those adhering to all the beneficial lifestyles and in addition consumed small to moderate quantities of alcohol would live still longer.

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7-2 BOLUS FIBRINOLYTIC THERAPY IN ACUTE MYOCARDIAL INFARCTION

In its early stage, acute myocardial infarction (**MI**) is associated with thrombotic coronary artery occlusion. Plasminogen activators dissolve the clots.

This article discusses the emergence of new bolus fibrinolytics (**BFs**) which are derived by molecular engineering from tissue-type plasminogen activator (alteplase; **tPA**). Phase 2 and phase 3 trials are in progress.

The 3 new "teplase" BFs are: reteplase; lanoteplase; and tenecteplase.

Conclusion: The new fibrinolytics produce similar outcomes and are easier to administer.

STUDY

1. Literature search selected 38 studies which evaluated the pharmacokinetics and pharmacodynamics of the 3 BFs.

RESULTS

1. Alteplase (the original tissue plasminogen activator — **tPA**) is given by bolus + infusion over 90 minutes.
2. Reteplase (**rPA**) is derived from tPA. It is produced in *E coli* cells.
3. Lanoteplase (**nPA**) is derived from tPA by deleting one amino-acid chain and mutating one amino-acid substitution.
4. Tenecteplase (**TNK-tPA**) is produced by altering tPA at 3 sites.
5. nPA and TNK-tPA are administered as a single bolus; rPA as a double bolus 30 minutes apart.
6. rPA is excreted by both kidney and liver; the other two by liver.
7. All three have a prolonged half-life compared with tPA. All are given with aspirin and heparin.
8. TNK-tPA is the most fibrin-specific. It reduces systemic fibrinogen and plasminogen levels to a lesser extent than the other 2.
9. rPA and nPA also degrade factor V and factor VIII. They may lead to a greater potential for bleeding.
10. TNK-tPA and rPA are comparable with tPA in terms of efficacy and safety. They are more convenient to administer.
11. nPA is effective, but the rate of intracranial hemorrhage is higher.

DISCUSSION

1. The simple bolus administration should shorten the time between onset of pain and treatment (onset-to-needle time). It should facilitate pre-hospital fibrinolysis.
2. The less complicated regimens will likely reduce medication errors and reduce mortality.
3. Intracranial bleeding is the most serious complication of fibrinolysis. It is a major disadvantage when compared with percutaneous coronary intervention. Reduced doses of heparin may lower the risk without compromising efficacy. The difference in risk of intracranial bleeding between the drugs awaits further investigation.
4. The thrombus obstructing the artery in ST-segment-elevation acute MI consists of several elements — platelets and thrombin in addition to fibrin mesh. Fibrinolytic agents target the fibrin, but are also associated with heightened thrombin activity and platelet activation. The glycoprotein platelet inhibitor, GPIIb/IIIa might be a logical addition to fibrinolytic therapy. A recent study reported equal efficacy of half dose rPA + the platelet inhibitor abciximab compared with full dose rPA. This combination may be safer.

CONCLUSION

Given the ease of administration and the similar outcomes compared with recombinant tPA, it is likely that a key component of reperfusion will include a bolus fibrinolytic.

JAMA July 25, 2001; 286: 442-49 Original investigation, first author Joan Llevadot, Brigham and Women's Hospital and Harvard Medical School, Boston Mass. www.jama.com

Comment:

I abstracted the article in anticipation of entry of at least some form of bolus therapy. Primary care clinicians who do not have immediate access to emergency department consultations should be able to administer the newer bolus treatments in the office, thus shortening the onset-to-needle time and greatly improving prognosis.

7-3 ALBUMINURIA AND RISK OF CARDIOVASCULAR EVENTS, DEATH, AND HEART FAILURE IN DIABETIC AND NON-DIABETIC INDIVIDUALS.

Microalbuminuria (dip-stick negative) albuminuria (**MA**) is a risk factor for cardiovascular disease. (**CVD**). It is present in about 30% of patients with diabetes, and in up to 15% of middle-aged individuals without diabetes. It is an independent predictor of future stroke, death, and myocardial infarction.

Whether individuals with albumin excretion rates below the MA threshold are also at risk for CVD or whether there is a progressive graded relationship between different degrees of albuminuria is not known.

This study examined the relationship between baseline albuminuria levels and future CVD events in patients without diabetes (**DM**) as well as those with diabetes.

Conclusion: Any degree of albuminuria was a risk factor for CVD events in individuals without DM as well as those with DM.

STUDY

1. The Heart Outcomes Prevention Evaluation study (HOPE)¹, a cohort study, followed over 5500 individuals.
2. All were over age 55. All had: 1) a history of CVD, or 2) DM with at least 1 additional CVD risk factor. None had dipstick-positive albuminuria or established diabetic nephropathy.
3. Measured albumin/creatinine ratio (ACR) in a first morning urine specimen at baseline, at 1 year, and at study end.
4. Defined microalbuminuria as an albumin/creatinine ratio of 2mg/mmol or more, provided the dipstick was negative for proteinuria. (*Microalbuminuria has also been defined as excretion of 30 to 300 mg daily, and as 20 to 200 ug/min.*)
5. Follow-up = 4.5 years.

RESULTS

1. Microalbuminuria as defined was detected in 33% of patients with DM and 15% of those at high risk but without DM.
2. Microalbuminuria increased the adjusted relative risks (RR):

Major CVD events	1.8
All cause death	2.1
Hospitalization for CHF	3.2
3. Results were similar for participants with and without DM. Those with MA were older, had higher BPs, a lower ankle/brachial systolic BP ratio, and a higher serum creatinine concentration.
4. Relative risk of the aggregate endpoint (cardiovascular events, all-cause death, and hospitalization for congestive heart failure) rose in a graded manner from the lowest quartile of MA (the lowest a/c ratio) to the highest quartile of MA (the highest a/c ratio). Quartiles of relative risk:

First (<0.22)	Second (0.22-0.57)	Third (0.58-1.62)	Fourth (>1.62)
1.0	1.1	1.4	2.0

DISCUSSION

1. MA was a strong independent risk factor for future CVD events, hospitalization for heart failure, and all-cause mortality in patients with diabetes and in those individuals without diabetes who have increased risk factors at baseline.
2. The risk extends well below the currently accepted screening threshold for diagnosis of MA.

3. These results support the suggestion that albuminuria reflects underlying vascular disease.
4. Patients with a higher absolute risk of CVD will experience a greater absolute risk reduction when given preventive interventions.
5. Albuminuria reveals increased renal endothelial permeability and may be an easily measured marker of diffuse endothelial dysfunction, and likely reflects underlying macrovascular and microvascular disease.
6. Cost of determining the albumin/creatinine ratio in urine is relatively inexpensive.

CONCLUSION

Any degree of albuminuria is a robust, independent risk factor for future cardiovascular events in individuals without DM who have increased risk factors for CVD, as well as those with DM. The risk increases as the albumin/creatinine ratio increases, starting well below the cutoff for microalbuminuria.

JAMA JULY 25, 2001; 286: 421-26 Original investigation, first author Hertz C Gerstein, HGH-McMaster Clinic, Hamilton, Ontario, Canada. www.jama.com

1 HOPE was the study demonstrating considerable benefit from the ACE inhibitor ramipril in high-risk patients. NEJM 2000; 342: 145- 53

Comment:

This is another example of what is becoming a general principle. There is no distinct cut point to separate risk from no risk. Risks from various indicators rise in a graded manner even in ranges below the low reference levels. This is so for LDL-cholesterol, body weight, abdominal circumference, blood glucose, blood pressure.

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7-4 ANGIOTENSIN-CONVERTING ENZYME INHIBITORS AND PROGRESSION OF NON-DIABETIC RENAL DISEASE: Meta-analysis of Patient-Level Data

Angiotensin-converting enzyme inhibitors (ACE) are effective in slowing progression of renal disease due to diabetes. No consensus exists about their effect on non-diabetic renal disease.

This study analyzed trials comparing efficacy of antihypertensive regimens including ACE to efficacy of regimens without ACE in non-diabetic renal disease.

Conclusion: ACE regimens were effective in slowing progression of non-diabetic renal disease.

STUDY

1. Performed literature search of studies (pooled individual patients = 1900; mean age = 52) evaluating effects of ACE on non-diabetic renal disease. Mean baseline values: BP = 148/86; creatinine = 2.3 mg/dL; urinary protein = 1.8 g/d
2. Worldwide, many cases of renal failure are not due to diabetes. This study included glomerular diseases, polycystic kidney disease, and hypertensive nephrosclerosis.
3. Determined differences in effects on renal function of antihypertension regimens containing ACE vs non-ACE regimens over a mean of 2.2 years. Non-ACE included diuretics, beta-blockers, calcium blockers, and alpha adrenergics.

RESULTS

1. Patients in the ACE groups had a greater decrease in mean BP (4.5/2.3 mm Hg).

2. And a lower excretion of protein by 0.5 g/d.
3. After adjustments, relative risks in the ACE group were 0.7 for end-stage renal disease, and 0.7 for the combined outcome of doubling of baseline creatinine concentrations and end stage renal disease.
4. Patients with greater urinary protein excretion at baseline benefited more.

DISCUSSION

1. "Our pooled analysis . . . reveals strong and consistent effects of ACE inhibitors in slowing progression of nondiabetic renal disease."
2. As in diabetic renal disease, ACE decreased BP, decreased urinary protein excretion, slowed the increase in serum creatinine, and reduced incidence of end-stage renal disease.
3. As in diabetic renal disease, a greater decrease in BP and urinary protein excretion was associated with lower risk of progression, but the beneficial effect of ACE was mediated by factors in addition to their effect on BP.
4. Chronic renal insufficiency is under-diagnosed and under-treated. Opportunities for prevention are lost. The presence of proteinuria in chronic renal disease is a strong indication for treatment with ACE.
5. "ACE inhibitors should be the antihypertensive agents of first choice in nondiabetic renal disease."
6. If BP and proteinuria remain elevated despite maximal ACE administration, other agents should be added.

CONCLUSION

Antihypertension regimens including ACE are more beneficial in slowing the progression of non-diabetic renal disease than regimens that do not contain ACE.

Annals Int Med July 17, 2001; 135: 73-87 Original investigation by the "ACE Inhibition in Progressive Renal Disease Study Group", first author Tazeen H Jafar, Aga Khan University, Karachi, Pakistan

www.annals.org

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7-5 PATIENT-INITIATED TREATMENT OF UNCOMPLICATED RECURRENT URINARY TRACT INFECTIONS IN YOUNG WOMEN

Urinary tract infections (UTIs) in younger women are a common outpatient problem. Recurrences often cluster and result in frequent office visits. They may require use of prophylactic antimicrobial agents. This study assessed the accuracy of self-diagnosis and feasibility of patient-initiated treatment of recurrent UTIs.

Conclusion: Women accurately self-diagnosed and self-treated recurrent UTIs.

STUDY

1. Uncontrolled, prospective trial entered 172 women over 18 years of age (mean = 23). All had a history of at least 2 UTIs in the past year. All were highly motivated and adherent.
2. They self-diagnosed recurrent UTI on the basis of symptoms, and self-treated with ofloxacin (*Floxin*) or levofloxacin (*Levoquin*) for 3 days.
3. Pretherapy urinalysis determined accuracy of self-diagnosis by culture, or sterile pyuria, or no alternative diagnosis probable.
4. Post-therapy interviews and urine cultures assessed clinical and microbiological cure rates, adverse effects, and patient satisfaction.

RESULTS

1. During a 12-month period, 50% self-diagnosed at least one episode of UTI .
2. In most cases culture showed a uropathogen. Some had only pyuria or bacteriuria. A few had no bacteriuria or pyuria and were diagnosed on the basis of no reasonable alternative diagnosis. Overall, the great majority (94%) of self-diagnosed episodes were UTIs reasonably requiring antimicrobial therapy.
3. Over 90% had clinical and microbiological cures from self-initiated therapy.
4. Almost all participants preferred this method of management. Few significant adverse events occurred.

DISCUSSION

1. Previous studies reported that each episode of UTI results in 6 symptomatic days as well as time lost from work.
2. In this study, over 90% of suspected UTIs met criteria for definite or probable UTI.
3. In primary care practice a urine culture would not be necessary. Young women with a history of recurrent UTIs would usually be treated empirically.

CONCLUSION

Motivated and adherent young women can accurately self-diagnose and self-treat recurrent UTIs.

Annals Int Med July 3, 2001; 135; 9-16 Original investigation, first author Kalpana Gupta,
University of Washington, Seattle www.annals.org

An editorial in this issue (p 51-2) by Andrew Herxheimer comments:

Patient self-management is widely used for some chronic diseases – eg, diabetes, asthma, gout, severe herpes simplex, common cold and low back pain. (*I could add osteoarthritis, migraine and other headaches, intermittent insomnia. Indeed, self-directed treatment is a standard practice in primary care. RTJ*)

Balint reminded us that the Latin word for “doctor” means “teacher”. His point was that we must help patients learn from their illness experiences and enable them to prevent what is preventable, and cope as well as possible with what cannot. Every encounter between a patient and physician is a learning experience for both, although the participants are rarely conscious of it.

7-6 THE EFFECT OF HORMONE REPLACEMENT THERAPY ON CARDIOVASCULAR RISK FACTORS IN TYPE 2 DIABETES.

The diabetic lipid profile consists of hypertriglyceridemia, raised very low-density lipoprotein (**VLDL**), and reduced HDL-cholesterol.

In non-diabetic women, menopause is associated with increased LDL-cholesterol. (Harmful effect)

Hormone replacement therapy (**HRT**) is associated with improvement in lipoprotein levels in non-diabetic women. (Beneficial effect)

This study concerned the effects of HRT on diabetic women.

Conclusion: In postmenopausal women with type 2 diabetes, HRT improved lipid profiles and some markers of coagulation.

STUDY

1. Randomized, controlled cross-over study enrolled 61 postmenopausal women. (Mean age = 64)

- Each subject received continuous HRT or placebo of 6 months, and then was crossed over. HRT consisted of conjugated equine estrogens (*Premarin*) 0.625 mg daily, and medroxyprogesterone (*Provera*) 2.5 mg daily. To minimize possible early acute adverse effects, HRT was started at a low dose and gradually increased to these levels over one month.
- Excluded patients with established coronary disease, severe diabetes, and very high total cholesterol levels.
- Measured lipid profiles fibrinogen, and HbA1c.

RESULTS

1. After 6 months (mean levels):	HRT	Placebo
Total cholesterol (mg/dL)	224	243
LDL-cholesterol "	139	158
HDL-cholesterol "	46	42 (not significant)
Triglyceride "	212	204 (not significant)
Lipoprotein (a) (U/L)	149	173
Glucose (mg/dL)	154	171
HbA1c (%)	7.6	7.6
Fibrinogen (mg/dL)	350	370

- The reduction in total cholesterol was accounted for mainly by the reduction in LDL.

DISCUSSION

- Combined HRT was associated with reduced levels of total cholesterol, LDL-cholesterol, Lp(a), and fibrinogen.
- The reduction in LDL was comparable to effects of regimens using only estrogen. This suggests that medroxyprogesterone does not attenuate the LDL-lowering effect of estrogen.
- Studies using estrogen alone have demonstrated a HDL-elevating effect. In this study, there was no significant increase in HDL. This may be due to an attenuating effect of the progestin.
- Triglycerides were not increased significantly by combined HRT. This is contrary to effects of estrogen in non-diabetic women. The lack of increase may be due to an improvement in insulin sensitivity. Other studies have reported that estrogen increases insulin sensitivity.
- No evidence in this study that risk of cardiovascular events increased during the HRT phase.

CONCLUSION

There is compelling evidence that HRT exerts beneficial effects on a number of cardiovascular risk factors in postmenopausal non-diabetic women. This study demonstrated beneficial effects on older women with type 2 diabetes.

Archives Int Med July 25, 2001; 161: 1772-76 Original investigation, first author Patrick J Manning, University of Otago, Dunedin, New Zealand. www.archinternmed.com

Comment:

This strengthens the belief that HRT ultimately reduces risk of CVD by improving lipid fractions in diabetic as well as non-diabetic women. RTJ

All diabetic women should receive antiplatelet therapy with low-dose aspirin. This would help attenuate a possible prothrombotic activity of HRT.

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7-7 POSTMENOPAUSAL HORMONE USE AND SECONDARY PREVENTION OF CORONARY EVENTS IN THE NURSES' HEALTH STUDY

The Heart and Estrogen/progestin Replacement Study (HERS)¹ randomized over 2500 women who had previously diagnosed coronary heart disease (CHD). (A secondary prevention trial.) During the first year of observation, women who took hormones had a 50% *increased* rate of major coronary events compared with women who took no hormones. During the second year, rates were equal. During the final fourth and fifth years those assigned to hormone therapy had a 33% *lower* risk of coronary events. Thus, the trial had overall null results of benefit. The overall results of HERS and the apparent changes in risk over time were unexpected.

This study examined the effects of duration of hormone therapy and explored the effect of different hormone regimens related to secondary prevention of major coronary events.

Conclusion: Over the short term, hormone users experienced an increase in risk of a second coronary event. Risk decreased with longer-term use to a level below that of never users.

STUDY

1. The prospective observational Nurses' Health Study began in 1976 entering over 121 000 women. Information was updated every 2 years for 20 years.
2. At onset, 248 postmenopausal women reported CHD. Over the years, over 2200 women who reported coronary disease were added.
3. Determined hormone replacement therapy (HRT) relating time of onset of HRT with time of the CHD event.

RESULTS

1. Short-term users of hormone therapy (< 1 year) had a 25% increase in recurrent coronary events.
(Relative risk 1.25 compared with never users.)

2. Long-term users had a decreased risk compared with never users:

	Relative risk
Never users	1.0 (referent)
< 1 year	1.25
1-2 years	0.55
> 2 years	0.38
All current users (overall)	0.65

3. Calculating the absolute risk:

If 100 000 women age 60-75 with coronary heart disease at baseline received hormone therapy, one would expect 420 *additional* recurrent coronary events in the first year of use. But 1040 *fewer* events per year during longer term use.

4. Short term risk (1 year) of an event was largely limited to the subset of women who originally began HRT after a first coronary event. (Relative risk = 2.1 compared with never users.) Risk of a second event after the first year declined (RR = 0.5) indicating a protective effect of hormones.
5. No clear difference between users of estrogen alone vs estrogen/progestin.

DISCUSSION

1. In this cohort of postmenopausal women who had established coronary disease, there was an apparent increased risk of

- a second major coronary event during the first year of use of hormone therapy.
2. During the 2nd year and after, risk declined to below that of never users.

CONCLUSION

The risk of recurrent major coronary events seemed to be increased among short-term hormone users with previous coronary disease. With continued use beyond 1 year, risk decreased to a level below the risk in non-users.

Annals Int Med July 3, 2001; 135: 135-38 Original investigation, first author Francine Grodstein, Brigham and Women's Hospital and Harvard School of Public Health, Boston Mass. www.annals.org

1 JAMA 1998;280:605 "Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Heart Disease in Postmenopausal Women" Heart and Estrogen/progestin Replacement Study (HERS)

Comment:

Following the HERS trial there has been much discussion and confusion regarding our advice regarding HRT. At present, the advice is not to use HRT primarily for prevention of coronary disease or stroke. (Actually, this was never a prime reason for use.) Certainly many women derive other benefits from HRT.

Evidence thus far indicates an early increase in risk possibly due to a thrombogenic effect of hormones and a later protective effect possibly due to improvement in lipid profiles and other beneficial effects of estrogen.

I believe primary care clinicians can reasonably give the following advice:

1. HRT should be started early in the premenopausal or immediate postmenopausal time period when women, because of their younger age, will have less risk of coronary events.
2. HRT might be avoided if possible even at an early age in women at high risk (eg, established coronary disease, smokers, lipid disorders, hypertension).
3. Women with troublesome menopausal symptoms who choose HRT might be started on low dose estrogen. (eg, 0.3 mg *Premarin*) augmented with low-dose prophylactic aspirin until the danger period of 1 year is passed.

7-8 RISK OF RECURRENT CORONARY EVENTS IN RELATION TO USE AND RECENT INITIATION OF POSTMENOPAUSAL HORMONE THERAPY

The recent Heart and Estrogen/progestin Replacement Study (**HERS**)¹ unexpectedly reported an *increase* in coronary heart disease (**CHD**) events during the first year of hormone replacement therapy (**HRT**). Compared with those not taking HRT, relative hazard (**RH**) = 1.5. Risk was highest in the first 4 months of therapy (**RH** = 2.3). There was *decreased* risk in years 4 and 5 (**RH** = 0.75). Over 4 years, no cumulative benefit occurred (also no cumulative harm) from HRT (**RH** = 0.99).

This present study also assessed risk of recurrent myocardial infarction (**MI**) related to HRT in women who had survived a first MI.

Conclusion: Results were consistent with HERS, an early transient increase in coronary risk followed by decreased risk.

STUDY

1. Population-based cohort study followed over 950 postmenopausal women. All had survived hospital discharge after their first MI. [A secondary prevention study.]
2. Obtained information on use of HRT and recurrent coronary events.
- 3 Follow-up = 3.5 years.

RESULTS

1. 186 recurrent coronary events occurred.
2. Overall, after 3.5 years and adjustment for possible confounders, there was no difference in risk of recurrent events between current hormone users and non-users. (RH = 0.96)
3. Comparing users with non-users, there was a suggestion of an increased risk of a recurrent event during the first 60 days after starting HRT. (RH = 2.2). For most of these women, this was the first recorded HRT use. (Ie, they were not receiving HRT at the time of their MI.)
4. Risk was slightly reduced among current HRT users during days 60 to 365. (RH = 0.92)
5. And a further reduction after 1 year. (RH = 0.76)

DISCUSSION

1. "In this 3.5 year observational study of women who survived to hospital discharge after a first myocardial infarction, there was no overall difference in the adjusted risk of recurrent coronary events between current users and current non-users of hormones."
2. There was a suggestion of increased risk during the first 60 days after starting or restarting HRT.
3. Compared with non-users, there was a suggestion of a *decreased* risk after 1 year of use. (Ie, possible benefit.)

CONCLUSION

After a first myocardial infarction, use of HRT was associated with a transient rise in risk of recurrent coronary events in the first 60 days. Thereafter, use of HRT (compared with non-use) was associated with a reduction in risk (ie, a benefit).

Archives Int Med July 23, 2001; 161: 1709-13 Original investigation, first author Susan R Heckbert, University of Washington, Seattle. www.archinternmed.com

1 "Randomized Trial of Estrogen Plus Progestin for Secondary Prevention of Coronary Heart Disease in Postmenopausal Women" JAMA 1998; 280: 605-13

Comment:

Any increased risk in women without coronary disease during the first months of HRT would be much lower than the risk reported in the recent secondary prevention studies. In women without coronary disease and without risk factors for coronary disease, it is reasonable to believe that HRT would be protective over the long run.

Women have been upset by recent reports in the media which state that HRT should not be used primarily to prevent coronary disease or stroke. (But HRT was never used primarily for this purpose.) I believe that women who opt for HRT should start at pre-menopause or menopause when their risk of coronary disease is lower because of their age. Starting HRT at an older age and by individuals with other risk factors of coronary disease would be riskier.

Starting estrogen at low dose (eg, 0.3 mg *Premarin*) for the first year would also likely be a little less risky. In addition, low-dose aspirin would be indicated. RTJ

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7-9 ANALGESIC USE AND RENAL FUNCTION IN MEN

High doses of analgesics, especially non-steroidal anti-inflammatory drugs (**NSAIDs**), have been implicated as a cause of acute renal failure. This occurs most commonly in patients with impaired renal function. The association between phenacetin and renal damage is strong. (Phenacetin was banned in the US in 1983.)

It has been suggested that prolonged use of analgesics including acetaminophen, aspirin, and NSAIDs may cause progressive renal damage.

This study of a large cohort of healthy men assessed the association of long-term use of analgesics with risk of renal failure.

Conclusion: Moderate use was *not* associated with increased risk of renal dysfunction.

STUDY

1. Cohort study of over 10 000 men in the Physician's Health Study¹ lasted over 14 years. All were considered healthy at baseline.
2. Conducted annual follow-ups. Determined self-reported use of acetaminophen (*Tylenol*) aspirin, and other NSAIDs.
3. Main outcome measures: 1) elevated creatinine defined as 1.5 mg (133 umol/L) or higher, or 2) creatinine clearance of 55 mL/min (0.9 mL/s) or lower.

RESULTS

1. A total of 460 men (4%) developed elevated creatinine levels; 11% developed reduced creatinine clearance.
2. Mean creatinine levels and creatinine clearances were similar among men who used analgesics vs those who did not.
3. Even at a total of 2500 or more pills, there was no difference in risk of kidney damage.

Relative risk acetaminophen	0.83
aspirin	0.98
other NSAIDs	1.07

4. No association between analgesic use and reduced creatinine clearance.

DISCUSSION

1. "In this large cohort study of initially healthy male physicians followed for an average of 14 years, we found no significant associations between the use of acetaminophen, aspirin, and other NSAIDs and either elevated creatinine levels or reduced creatinine clearance."
2. There was no association in men who used over 2500 pills (mean of 3 to 4 a week).
3. There was no increased risk among higher-risk groups such as those over age 60, or those with hypertension or diabetes.
4. This result contrasts with some previous case-control studies.

CONCLUSION

This provides reassurance that there is *not* a strong relationship between chronic moderate use of acetaminophen, aspirin, and other NSAIDs and development of renal disease in persons with normal renal function.

JAMA July 18, 2001; 286: 315-21 Original investigation, first author Kathryn M Rexrode, Channing Laboratory, Brigham and Women's Hospital, Boston Mass. www.jama.com

- 1 This is the study which reported benefit from aspirin as a primary prevention of myocardial infarction.

Comment:

This does *not* provide reassurance among those with initial renal dysfunction. NSAIDs in these patients may lead to further kidney dysfunction.

Primary care clinicians must remember that NSAIDs can have a deleterious effect on patients with heart failure and hypertension through their pharmacological effect on the kidney. RTJ

7-10 A PROSPECTIVE STUDY OF PHYSICAL ACTIVITY AND COGNITIVE DECLINE IN ELDERLY WOMEN.

Several studies have suggested that physical activity is positively associated with the cognitive function of elderly persons.

This prospective study asked: is physical activity associated with cognitive decline in elderly women.

Conclusion: Women with higher levels of activity were less likely to develop cognitive decline.

STUDY

1. Entered 6000 community-dwelling women all over age 65. None had cognitive impairment or physical limitations at baseline.
2. Measured cognitive performance using a modified Mini-Mental State Examination.
3. Measured daily activities and recreational activities by self-reported blocks walked per week and by total kilocalories expended per week in recreation (blocks walked and stairs climbed).
4. Repeated mental examination 6 to 8 years later.

RESULTS

1. Women with greater physical activity at baseline were less likely to experience cognitive decline. 17% of women in the greatest activity quartile had a 3-point decline of cognition vs 24% of those in the lowest quartile.
2. After adjustment for possible confounders, the odds ratio for cognitive decline in the highest physical activity group was 0.7 compared with those in the lowest activity group.

DISCUSSION

1. Women who had greater baseline physical activity, whether measured by blocks walked or total kilocalories expended per week, were less likely to develop cognitive decline over 6 to 8 years.
2. Moderate, as well as strenuous physical activity was associated with decreased risk.
3. The association was not explained by differences in baseline function or health status.
4. Although the exact mechanism is not known, regular physical activity may reduce serum-lipid levels and hypertension, and increase cerebral blood flow, all of which could reduce risk of vascular dementia and Alzheimer's disease.

CONCLUSION

Elderly women with higher levels of baseline physical activity were less likely to develop cognitive decline over the next 6 to 8 years.

Archives Int Med July 23, 2001; 161: 1703-08 Original investigation, first author Kristine Yaffe, University of California, San Francisco. www.archinternmed.com

7-11 ACUTE EFFECTS OF PASSIVE SMOKING ON THE CORONARY CIRCULATION IN HEALTHY YOUNG ADULTS.

Passive smoking is a risk factor for ischemic heart disease (**ISD**). It may be associated with vascular endothelial dysfunction.

This study determined the acute effects of passive smoking on the coronary circulation by non-invasive transthoracic Doppler echocardiography.

Conclusion: Passive smoking substantially reduced coronary flow velocity.

STUDY

1. Cross sectional study of 30 Japanese men (mean age 27) entered 15 healthy non-smokers and 15 asymptomatic active smokers. The non-smokers had no history of exposure to tobacco smoke.
2. Measured coronary blood flow velocity reserve (**CBFVR**) in the left anterior descending artery. CBFVR is the ratio of hyperemic to basal coronary flow velocity when the hyperemia is induced by intravenous adenosine. (This is a measure of endothelial function. Adenosine causes dilation of the coronary arteries, increasing blood flow velocity. The study did not actually measure coronary blood flow.)
3. Measured each participant before and after a 30 minutes exposure to environmental tobacco smoke.

RESULTS

1. Heart rate and BP were not affected by the adenosine in either group.
2. Before passive smoke:

At baseline, CBFVR (increase in velocity after adenosine) was significantly lower in the smokers vs the non-smokers. (I.e, smokers had less capacity to dilate when given adenosine.)

3. After passive smoking:

Passive smoke exposure significantly reduced mean CBFVR in non-smokers but not in smokers.

(In non-smokers, the 30 minute exposure to smoke reduced the capacity of the coronary artery to dilate. The CBFVR in smokers did not decrease at all after passive smoke inhalation. They were already at a state where the passive smoke had no effect in addition to the effect of recent smoking.)

4. Carbon monoxide levels rose in the non-smokers, did not rise in smokers. It was already at a high baseline level.

DISCUSSION

1. Temporary passive smoke inhalation abruptly reduced coronary blood flow reserve in non-smokers, but did not affect active smokers. (Their system is saturated.) This provides direct evidence of a harmful effect of passive smoking on the coronary circulation.
2. Impaired coronary flow reserve has been suggested as a surrogate measure of subclinical coronary atherosclerosis. It provides an integrated measure of both vascular endothelial function and smooth muscle relaxation.
3. After exposure to passive smoke, the CBFVR in non-smokers was reduced to the same level as in active smokers.
4. Carbon monoxide levels rose after passive smoke exposure in non-smokers, but was unchanged in smokers. This is likely to increase the harmful effects on non-smokers.

CONCLUSION

Passive smoking substantially reduced coronary blood flow reserve in healthy non-smokers. Passive smoking may cause endothelial dysfunction in the coronary circulation in non-smokers.

JAMA July 25, 2001; 286: 436-41 Original investigation, first author Ryo Otsuka, Osaka City University Medical School, Osaka, Japan www.jama.com

An editorial in this issue (p 462) by Stanton A Glantz, and William W Parmley comments:

Endothelial dysfunction may be at the heart of development of atherosclerosis. Normal endothelial cells promote vasodilation and inhibit atherosclerosis and thrombosis in part because of the release of nitric oxide. Dysfunctional cells contribute to vasoconstriction, atherogenesis and thrombosis.

Platelet activation is another adverse effect of passive smoke.

Reduction in risk factors improves endothelial function and clinical coronary events. For example, in patients with hyperlipidemia, lipid control improves endothelial function.

The study helps explain the relatively large risk of death and other cardiac events associated with passive smoking, an increase of about 30%. Active smoking doubles risk.

Most people think of cancer of the lung in relation to active and passive smoking. Heart disease is an important consideration as well.

"Everyone should be protected from exposure to secondhand smoke."

Comment:

This should help change the minds of diehards who still maintain that harms of passive smoking are not proven. It strengthens the resolve of those who oppose smoking in public places. I wonder, does exposure to other air pollutants also increase risk? RTJ

7-12 MANAGEMENT OF SUSPECTED DEEP VEIN THROMBOSIS IN OUTPATIENTS USING CLINICAL ASSESSMENT AND D-DIMER TESTING

"When deep venous thrombosis is suspected, objective testing is required to confirm or refute the diagnosis."

D-dimer is released into the circulation when cross-linked fibrin is degraded by plasmin. Patients with deep venous thrombosis (DVT) usually have elevated D-dimer levels. A normal level can help exclude DVT.

This study determined the likelihood of DVT in patients with varying degrees of pretest clinical probability of DVT followed by a D-dimer test.

Conclusion: Combinations of low probability + negative D-dimer ruled out DVT.

STUDY

1. Prospective cohort of 445 symptomatic patients referred for suspected first episode of DVT.
2. Categorized patients initially as low, moderate, or high probability of having DVT.
3. Clinical factors included in the assessment of DVT (pretest):¹
 - Objective leg swelling
 - Pain on palpation of deep vein regions
 - Elevated pulse rate (> 100)
 - Immobilization
 - Recent surgery
 - Previous DVT or pulmonary embolism
 - Malignancy
4. Correlated results of bedside D-dimer test² (positive or negative) with clinician's assessment of pretest probability.

5. Presence or absence of DVT was established by venography and ultrasound. Follow-up = 3 months.

RESULTS

1. Prevalence of DVT

D-dimer	Pretest probability		
	Low	Moderate	High
Negative	1 of 177	7 of 120	2 of 8
Positive	4 of 29	17 of 68	33 of 41

2. Patients who had a low pretest probability and a negative D-dimer were highly unlikely to have DVT on a 3-month follow-up. Only one of 177 such patients developed DVT during follow-up. These patients did not receive anticoagulation.

DISCUSSION

1. "This study shows that it is safe to withhold further diagnostic testing and anticoagulant therapy in patients with 1) a low pretest probability of DVT and 2) a negative D-dimer test."
2. The likelihood of false negative and false positive D-dimer tests make the test unhelpful in the other categories of pretest probability.

CONCLUSION

The combination of a low pretest probability of DVT and a negative D-dimer test rules out DVT.

Annals Int Med July 17, 2001; 135: 108-111 Original investigation, first author Clive Kearon, McMaster Clinic, Hamilton, Ontario, Canada www.annals.org

1 See an accompanying article "Excluding Pulmonary Embolism at the Bedside without Diagnostic Imaging" Annals Int Med July 17, 2001: 135: 98-107.

2 Several different test kits are available. The study used the SimpliRED, AGEN Biomedical, Brisbane Australia.

It can be used at the bedside, and results (positive or negative) are read in a few minutes. This test has a high sensitivity and a low specificity for D-dimer. This results in a higher frequency of false positive tests.

Comment:

Clinicians undoubtedly vary in their assessment of pretest probability. Nevertheless, a reasonable consensus must exist.

Note, the D-dimer was not shown to be helpful when the pretest clinical probability of DVT was considered moderate or high. There were too many false negative and false positive tests. The study concludes the test is helpful only in patients with low pretest probability in ruling out DVT. In these patients, a negative D-dimer test will lead to avoidance of further diagnostic procedures and anticoagulation.

I can think of one practical application. Individuals after completing a long air flight in the "economy class" may complain of leg swelling and discomfort. Some will have DVT and even pulmonary embolism, especially after long flights. A quick D-dimer test may rule out further concern.

REFERENCE ARTICLE

7-13 SUBCLINICAL HYPOTHYROIDISM

(I abstracted a few points for emphasis, and a few I did not know or had forgotten. RTJ)

Routine screening often uncovers patients with very mild thyroid dysfunction. They have normal serum thyroxine and triiodothyronine levels, and mildly elevated thyrotropin (TSH) concentrations. Although "subclinical hypothyroidism" is the term most often used to describe the condition, "mild hypothyroidism" might be a more suitable term because on close questioning many patients disclose mild, non-specific symptoms.

Most of these patients have TSH levels of 5 to 10 mU per liter, a modest increase. Over half have elevated antibodies against thyroperoxidase. Goiter is twice as prevalent as in the general population.

Routine screening, especially older women has been advocated, although not endorsed unanimously because the benefits of subsequent therapy have not been established in prospective trials. However, a decision and cost-effectiveness model calculated that screening women over age 35 every 5 years would be beneficial. Half the benefit would be from prevention of subsequent overt hypothyroidism, 30 percent for improved symptoms, and a smaller benefit from improvement in serum lipids. In addition, because undetected subclinical hypothyroidism during pregnancy may adversely affect the fetus and can be associated with hypertension and toxemia in the mother, screening pregnant women has been advocated. Data suggest ovulatory dysfunction and infertility may be associated.

The effects of therapy have been debated for decades. Prevention of progression to overt hypothyroidism has been found to be about 4% per year in women with both an elevated TSH and antithyroid antibodies. (38 times that of women with normal values.) The NNT to prevent one patient from developing overt hypothyroidism = 4 to 14. Benefit of treatment on serum lipids is debated. Rates of death from cardiovascular disease are not much different in treated women than in the general population. Some trials have reported improvements in mood and cognition after treatment.

There are arguments against treatment, mainly the danger of overtreatment causing atrial fibrillation and osteopenia.

Although disagreement persists, the author recommends screening and treatment because of the risk of progression to overt hypothyroidism. However, if the TSH is below 10, and the patient has no symptoms, no goiter, no LDL-cholesterol elevation, and is not pregnant and has no ovulatory dysfunction, she may be observed without therapy.

" I believe that the evidence supports the use of treatment for most patients, as long as therapy is monitored with annual measurements of serum thyrotropin."

NEJM July 26, 2001; 345: 260-65 "Clinical Practice", review article by David S Cooper, Johns Hopkins University School of Medicine, Baltimore MD. www.nejm.org

7-14 CAM RESEARCH ATTEMPTS TO SEPARATE WHEAT FROM CHAFF

The National Center for Complementary and Alternative Medicine (NCCAM) is part of the National Institutes of Health. NCCAM is attempting to develop a more thorough understanding of how herbs react in the body.

At present, use of CAM therapies is based more heavily on anecdotes and advertisements than on evidence.

CAM is being taken seriously in the biomedical world. Patient demand for information is one reason. An international conference meeting in San Francisco in May attracted over 300 abstracts and more than 400 participants representing 14 countries

One trial NCCAM is sponsoring is a multicenter, randomized, double-blind, placebo-controlled study comparing the effect of glucosamine and chondroitin with the COX-2 inhibiting-COX-1 sparing anti-inflammatory drug celecoxib (*Celebrix*) on osteoarthritis of the knee.

Another study will evaluate the use of the chelating agent, ethylene diamine tetra-acetic acid, in treating coronary disease.

There is growing evidence that some CAM products do indeed have pharmacological effects, some of which may be harmful. St. John's wort reduces levels of the protease inhibitor indinavir used in treating AIDs. Ginko biloba coats platelets preventing

adhesion to collagen, impeding clot formation. Ginseng may enhance the response to influenza vaccine as well as improve IgA mucosal immune responses.

JAMA July 11, 2001; 286: 156-58 "Medical News and Perspectives", commentary by Rebecca Voelker, JAMA staff.

www.jama.com

Comment:

Old timers will remember the days when digitalis was prescribed as pills containing digitalis leaf. There were attempts to standardize the preparations by something called "cat units". Not too long thereafter, digitoxin and digoxin were extracted and purified, allowing accurate dosing of these known-to-be active drugs. There are undoubtedly active compounds in herbal medicines which will be identified, purified, and added to the list of useful drugs. Harmful compounds in herbal preparations will also be identified. RTJ

See the following abstract. RTJ

7-15 HERBAL MEDICINES AND PERIOPERATIVE CARE.

Morbidity and mortality associated with herbal medications may be more evident in the perioperative period because of the polypharmacy and physiological alterations that occur during that time.

These investigators identified 8 commonly used single-herbal medicines that potentially pose the greatest impact to the care of patients undergoing surgery. The 8 account for about half of all single herbal medications among the 1500 sold in the US. Use is widespread among presurgical patients.

Can these herbal medicines have a negative impact on perioperative care?

Conclusion: Potentially serious problems may be associated with their use.

STUDY

1. Literature search selected studies addressing the safety and pharmacology of 8 most commonly used herbal medications for which pertinent safety information was available.
2. These include: echinacea, ephedra, garlic, ginkgo, ginseng, kava, St. John's wort, and valerian.
3. Non-herbal dietary supplements were excluded (vitamins, hormones, amino acids). Also excluded nonherbal medicines such as chondroitin and glucosamine which appear to be safe.

RESULTS

1. Complications in the perioperative period can arise from these herbs — direct actions as well as pharmacodynamic or pharmacokinetic effects.
2. Direct effects include bleeding from garlic, ginkgo, and ginseng; cardiovascular instability from ephedra; and hypoglycemia from ginseng.
3. Pharmacokinetic herb-drug interactions include potentiation of the sedative effect of anesthetics by kava and valerian.
4. Pharmacodynamic herb-drug interactions include increased metabolism of many drugs used in the perioperative period by St. John's wort.
5. (See table 1 p 213)

DISCUSSION

1. In 1997, about 12% of the US population used herbal medicines. "Patients undergoing surgery appear to use herbal medicines significantly more frequently than the general population." Most fail to disclose their use.
2. "Empirical evidence from a long history of herbal medication use supports the notion that most are safe. Nevertheless, some have been associated with serious harm."
3. The prevention, recognition, and treatment of complications begin with explicitly eliciting and documenting history of use. Familiarity with adverse effects as documented in the scientific literature is necessary because current US regulations for commercial preparations sold in the US do not protect the population against undesirable effects. Adverse effects are underreported.
4. A history of herbal medicine use should prompt physicians to suspect the presence of undiagnosed disorders causing symptoms that lead to self-medication. This includes children whose caretakers may prescribe herbs.
5. These herbs should be discontinued before surgery. There is a potential danger of adverse effects.
6. The task of caring for patients who use herbal medicines is an evolving challenge. The limited evidence-based information about their safety and efficacy and the absence of standard regulatory mechanisms for approval and surveillance, and improper patients assumptions, represent important medical issues. Physicians should be familiar with all medications, herbal or conventional, patients are taking in order to prevent, recognize, and treat potential serious problems associated with their use.
7. *The article lists several sites on the World Wide Web relating to herbal medicines and supplements.*

CONCLUSION

Many potential adverse effects may occur in patients taking herbal medicines before surgery.

During the perioperative evaluation, physicians should explicitly elicit and document a history of herbal medicine use. Physicians should be familiar with potential adverse effects in order to recognize, prevent, and treat serious problems associated with their use.

JAMA July 11, 2001; 286: 208-16 Original investigation, first author Michael K Ang-Lee, University of Chicago, Ill.

www.jama.com

Comment:

These cautions apply to primary care practice as well as to surgery. Herbal medicines are much more than placebos. Many are powerful pharmacological agents. Why do most main-line physicians object to their use?

1. Herbs are not standardized. They may contain multiple active components the effects of which are not known.
2. Potency may vary from batch to batch, and from manufacturer to manufacturer.
3. They may be misidentified or deliberately mislabeled or replaced with cheaper and more readily available alternatives.
4. May be adulterated with toxic substances or even conventional drugs.
5. Adverse effects may occur when combined with standardized drugs.
6. There is no mechanism for postmarketing surveillance.

7-16 EXTENDED-DURATION PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM AFTER TOTAL HIP OR KNEE REPLACEMENT

The optimum duration of anticoagulant prophylaxis after hip and knee surgery is uncertain. A common practice is to continue until discharge from the hospital, usually for 7 to 14 days. However in patients receiving in-hospital prophylaxis, the frequency of

venographic deep vein thrombosis (DVT) is up to 30% at hospital discharge. An additional 10-25% develop new DVT during the next 3 to 4 weeks.

This study aimed to establish the efficacy of extended-duration prophylaxis in patients undergoing elective hip and knee replacement surgery.

Conclusion: Extending prophylaxis for 30 to 42 days after hospitalization significantly reduced frequency of symptomatic DVT.

STUDY

1. Meta-analysis of randomized trials included 4000 patients. Nine trials met the authors' inclusion criteria. Eight used low molecular weight heparin; one, unfractionated heparin.
2. Out-of-hospital antithrombosis was continued for 30 to 42 days.
3. Compared incidence of DVT in patients receiving heparin vs placebo or no antithrombotic therapy.

RESULTS

1. Incidence of DVT during out-patient follow-up of 30-42 days:

	Heparin	Placebo	Absolute difference	NNT
Symptomatic DVT	1.3%	3.3%	2%	50
Asymptomatic DVT	10%	20%	10%	10

(By venography, ultrasound, or impedance plethysmography.)

2. No increase in major bleeding; 3.7% vs 2.5% incidence of minor bleeding. [Number needed to treat to harm 1 patient = 83.]

DISCUSSION

1. Extending duration of prophylaxis with heparin after hip or knee replacement for 4 to 6 weeks after hospitalization significantly reduced risk of DVT over a subsequent month.
2. There was an increase in the risk of minor, not major bleeding.
3. The risk of DVT in patients undergoing knee replacement was greater than those undergoing hip replacement possibly because of more extensive disruption of soft tissue and bone, and greater release of prothrombotic tissue factors.
4. Most DVT remains symptomless.
5. The authors estimate that routine use of extended-duration prophylaxis would prevent about 20 episodes of symptomatic DVT for every 1000 elective surgeries and one fatal case of pulmonary embolism for every 1000.
6. Low-molecular-weight heparin costs about \$25 per day.
7. There is emerging data that aspirin might be effective for prevention of DVT after hip fracture.

CONCLUSION

Among patients undergoing elective hip and knee replacement, outpatient LMW heparin continued for 4 to 6 weeks after discharge from hospital reduced the frequency of DVT.

Lancet July 7, 2001; 358: 9-15 Original investigation, first author John W Eikelboom, Royal Perth Hospital, Perth, Australia.

www.thelancet.com

Comment:

For situations in which warfarin or heparin is not feasible, aspirin certainly should be considered an option. RTJ

7-17 THREE MONTHS VERSUS ONE YEAR OF ORAL ANTICOAGULANT THERAPY FOR IDIOPATHIC DEEP VENOUS THROMBOSIS.

The optimal duration of treatment with oral anticoagulant agents after deep venous thrombosis (DVT) reflects a balance between the risk of recurrence when treatment is discontinued and the risk of bleeding resulting from continued anticoagulant therapy.

Patients who have thrombosis in absence of known risk factors (ie, idiopathic) or in association with persistent risk factors (eg, cancer; thrombophilia) are at higher risk of recurrence than patients with time-limited, reversible risk factors. Oral anticoagulation in the latter group can be limited to 3 months after elimination of the risk factor. More prolonged courses of therapy are recommended for patients whose thrombosis is associated with persistent risk factors. In addition, prolonged therapy may be indicated in patients with idiopathic thrombosis.

This study asks: In patients with idiopathic thrombosis, what is the risk of recurrent thrombosis when continuing anticoagulation therapy for an additional 9 months after the 3 month period? Will the additional duration of therapy protect against recurrence?

Conclusion; No – recurrence was still frequent after a total of 12 months anticoagulation.

STUDY

1. Followed patients with a first episode of idiopathic DVT (n = 267). All had been treated with a 3 month course of oral anticoagulation.
2. Randomly assigned to: 1) discontinuation of anticoagulation, or 2) continuation for an additional 9 months.
3. Follow-up for an additional 2 years to determine recurrence of symptomatic DVT.

RESULTS

1. Recurrence of DVT over an average follow-up of 38 months:

After additional 9 months of therapy	Therapy discontinued after 3 months
16%	16%
2. Of the 134 patients who continued anticoagulation, only 1 patient had a recurrence of DVT while receiving oral anticoagulants during months 4 to 12. Of the 133 who discontinued after 3 months, 11 had a recurrence during months 4 to 12. (Ie, continuing anticoagulation did prevent DVT during the treatment period.)
3. Three % of patients experienced major bleeding during the extended period of anticoagulation.

DISCUSSION

1. In patients with idiopathic DVT, continuing anticoagulation for 1 year after an episode of DVT decreased incidence of DVT during that time. However, after discontinuing anticoagulation, the recurrence rate of DVT was similar to that of patients who discontinued after 3 months. Prolonged anticoagulation in patients with idiopathic DVT simply delayed recurrence until after anticoagulation therapy was stopped.
2. Most recurrences occurred within the first year after discontinuation.
3. These results apply only to patients with idiopathic (apparently spontaneous) DVT.
4. All recurrences were also idiopathic. More than half involved the initially *unaffected* leg. This suggests a persistent underlying hypercoagulable state.

5. The recurrent events likely could be prevented by continuing anticoagulation indefinitely. This would bring a continuing risk of bleeding and costs of therapy.

CONCLUSION

In patients with acute idiopathic DVT, continuing anticoagulation for 1 year reduced recurrence during that year. However, after discontinuing anticoagulation, thrombosis recurred at a rate similar to the rate in those who discontinued after 3 months.

NEJM July 19, 2001; 345: 165-69 Original investigation by the Warfarin Optimal Duration Italian Trial Investigators, first author Giancarlo Agenli, Universita di Perugia, Italy. www.nejm.org

Comment:

If the decision is made not to continue warfarin, these patients should be placed on continuous aspirin. RTJ

7-18 A 28-YEAR OLD WOMAN WITH PANIC DISORDER

(I enjoyed this "refresher course". I abstracted a few highlights for emphasis, as well some points I did not know or had forgotten. RTJ)

The article begins by describing a young woman with typical symptoms of panic attacks which occurred frequently enough to qualify the diagnosis of "panic disorder".

A panic attack (**PA**) is defined as a discrete period of intense fear or discomfort accompanied by at least 4 out of 13 typical symptoms. PA develops abruptly and peaks in intensity within 10 minutes

Panic disorder (**PD**) is diagnosed in a patient with multiple recurrent unexpected panic attacks followed by persistent concern about recurrences, worry about implications of attacks and their consequences, and a significant change in behavior related to the attacks.

More than 3% of the population suffer from PD. Some may miss work and stop driving.

Most authorities believe PD occurs in genetically predisposed individuals who are exposed to significant life stress.

Adult patients with PD fear being alone. They avoid places from which exit would be delayed or impossible. ("agoraphobia") In worse case situations a patient may refuse to go anywhere unless accompanied by someone who can take them to the nearest emergency department. They are less likely to experience PA if a trusted companion is present.

A high rate of comorbidity with other psychiatric illnesses occurs in patients with PD. Patients frequently have anxiety disorders, including social anxiety disorder and generalized anxiety disorder. Substance abuse is more common than in the general population. And as many as 70% will have depression some time in their lives. Suicide attempts may be more common in patients with PD and associated depression.

The primary care clinician's main concern is to rule out potentially life-threatening medical illness.¹ PD should not be a diagnosis of exclusion. It should be included in the initial differential diagnostic scheme. Otherwise, patients tend to be told at the end of a lengthy evaluation "there is nothing wrong that we can find". This delays diagnosis and treatment. Diagnosis is aided by a family history of mood and anxiety disorders and recent significant life stress in the patient. Many patients will identify stressors.

The diagnosis is made by history. Although laboratory tests can rule out medical conditions masquerading as PD, there is no definitive test to confirm the diagnosis. Because of a close relationship with the patient, the primary care clinician is often the best person to suggest the diagnosis. PD can be explained as a medical condition characterized by excessive activity of parts of the

brain that control fear and autonomic nervous system responses. The cause is not known, but treatment is almost always successful. The clinician can acknowledge the reality of the symptoms and the terror they produce. This may encourage the patient to engage in a rational process of medical work up, ending in the diagnosis of PD.

Treatment: Establishment of an excellent physician-patient relationship is critical for treatment to proceed. Cognitive behavioral therapy (CBT) and medication are equally effective. About 70% will respond to CBT, but it requires specific training. Drug therapy can and should be prescribed by the primary care physician. (See table p 454) Benzodiazepines are effective (eg, clonazepam; *Klonopin*; generic), but they are rarely used as monotherapy. Antidepressants should be prescribed simultaneously. Selective serotonin reuptake inhibitors (SSRIs; eg, paroxetine; *Paxil*) are first-line drugs. The consultant prefers antidepressants, and avoids benzodiazepines unless the patient is wracked with anxiety. He does not consider benzodiazepines as definitive therapy. If used, clonazepam is first choice because it is the easiest to stop and is effective in low doses.

JAMA July 25, 2001; 286: 450-57 "Clinical Crossroads" review article by Jack M Gorman, Columbia University, New York.
www.jama.com

1 Eg, myocardial infarction, cardiac arrhythmias, hyperthyroidism, pheochromocytoma, asthma, substance withdrawal.

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7-19 PROPHYLAXIS WITH SINGLE-DOSE DOXYCYCLINE FOR THE PREVENTION OF LYME DISEASE AFTER AN *IXODES SCAPULARIS* TICK BITE

Lyme disease is the most common vector-borne disease in the US. It may be prevented by vaccination, although it is less than 100% effective. General acceptance of the vaccine is likely to be limited.

This study asks — can antibiotic prophylaxis prevent Lyme disease? Can antibiotic agents effectively cure incubating *Borrelia burgdorferi* infection?

Conclusion: A single dose of doxycycline can prevent development of Lyme disease.

STUDY

1. Randomized, double-blind, placebo-controlled trial conducted in a hyperendemic area of New York entered 482 subjects.
All had removed an attached *Ixodes* tick from their bodies within the previous 72 hours. The species and stage of the ticks were determined by a medical entomologist.
2. Randomized to 1) a single 200 mg dose of doxycycline, or 2) placebo.
3. Primary endpoint = development of erythema marginatum at the site of the tick bite.
Secondary endpoints = development of erythema migrans at a site different from the area of the bite, and serological evidence of infection.

RESULTS

1. Characteristics

Nymphal ticks

Partially engorged — 16%

Mean estimated duration of attachment — 30 hours

Adult ticks

Partially engorged — 6%

Estimated duration of attachment — 14 hours.

2. Erythema migrans developed in 1% of those receiving doxycycline vs 3.2% of those receiving placebo.
3. Erythema migrans developed more frequently after untreated bites from nymphal ticks than from adult bites (6% vs 0%).
Only ticks partially engorged with blood were associated with development of erythema migrans. This may have been related to the shorter period of attachment of the better recognized adults.
4. Objective extracutaneous manifestations of Lyme disease did not occur in any subject. There were no seroconversions.

DISCUSSION

1. Prophylaxis with a single dose of doxycycline given within 72 hours of a recognized bite from *Ixodes* was highly effective in preventing development of Lyme disease.
2. Erythema migrans at the site of the bite is the most common clinical manifestation.
3. Subsequent tick bites are common, reported by 18% of the subjects questioned.
4. Nausea and vomiting were common in the doxycycline group. Taking the drug with food may improve tolerability.

CONCLUSION

A single dose of doxycycline given within 3 days of a recognized tick bite prevented development of Lyme disease.

NEJM July 12, 2001; 345: 79-84 Original investigation by the Tick Bite Study Group, first author Robert B Nadelman, New York Medical College, Valhalla, NY www.nejm.org

An editorial in this issue of NEJM (pp 133-34) by Eugene Shapiro, Yale University School of Medicine comments:

The study confirms that the risk of Lyme disease is low (in this study 3%) after a deer tick bite even in a region where incidence is among the highest in the world.

Ticks must be at least partially engorged with blood (ie, must feed for hours) before *B burgdorferi* is transmitted. Incidence of erythema migrans was about 10% if the tick was partially engorged. If the tick had fed for over 3 days, the risk of Lyme disease rose to about 25%.

Prophylaxis might be stratified according to risk. If the risk of Lyme disease is about 3%, it would be necessary to give doxycycline to about 40 patients to prevent one case. (If the absolute benefit is $3.2\% - 1\% = 2.2\%$) And this would apply only to areas of high endemicity. Most tick bites in the US are due to the Lone star tick *Amblyomma americanum* and others that do not transmit Lyme disease.

However, in normal practice, it is difficult to know the species, stage, and degree of engorgement of the tick. "Ticks" identified by physicians may in fact be beetles, bugs, lice, spiders, or even just debris.

Anxiety about Lyme disease may be the most potent factor for demands for chemoprophylaxis. Publicity in the media and on the Internet has increased fears of Lyme disease out of proportion to its actual morbidity. This is compounded by the high frequency of misdiagnosis of Lyme disease in persons with chronic symptoms from other causes.

Who should receive prophylactic doxycycline?

Persons bitten by ticks in endemic areas.

The tick is at least partially engorged.

The tick is a nymphal deer tick.

In far more common circumstances, the risk of Lyme disease is so low that prophylaxis is not indicated.

"There is substantial evidence that in the vast majority of patients with Lyme disease conventional treatment with antimicrobials is very effective, and the long-term outcomes are excellent." Patients should be so advised.

The potential risks and benefits should be discussed with the patient, who should be involved in making the decision about prophylaxis. In any case, patients should be instructed to seek treatment if an expanding erythematous rash develops.

Comment:

NEJM considered this article important enough to fast-track it on its web site.

I suspect that most patients in highly endemic areas will insist on prophylaxis, given that only one dose is required, and that the risk of adverse effects is low. In most cases the physician will consider the risk of the disease to be very low, but will acquiesce to the patient's demands, especially those of an anxious mother. In these cases, doxycycline is really administered as a placebo. RTJ

"Lyme Disease" a long review article in this issue NEJM July 12, 2001; 345: 115 -125 comments:

In the past decade, the complete genome of the spirochete has been sequenced. Animal models have been developed for studies of pathogenesis. Guidelines for diagnosis, and treatment have been established and a vaccine developed.

There is an illustration of the nymphal tick on p 118. It is an almost invisible black speck. I wonder how the investigators of the study found so many subjects with nymphal tick bites. Illustrations of erythema migrans appear on pp 118 and 119.

A case definition appears on p 120; treatment and vaccinations regimens on p 122.

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