

PRACTICAL POINTERS FOR PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JUNE 2000

COLONOSCOPY — THE BEST SCREEN FOR CA OF COLON

FLAT COLON NEOPLASMS ARE COMMON AND DANGEROUS

LOW-MOLECULAR-WEIGHT HEPARIN FOR ACUTE CORONARY SYNDROMES

MANAGEMENT OF ACUTE CORONARY SYNDROMES

TRAINING CHILDREN TO AVOID DOG BITES

STATIN DRUGS REDUCE RISK OF FRACTURE IN OLDER WOMEN

STATIN DRUGS INCREASE BONE MINERAL DENSITY

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ACUTE CHEST PAIN PATIENTS AND MISSED MYOCARDIAL DAMAGE

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SUICIDAL BEHAVIOR IN GAYS

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EXERCISE TRAINING FOR CHRONIC HEART FAILURE.

REFERENCE ARTICLES

RECOMMENDED READING

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HIGHLIGHTS JUNE 2000

6-1 A COMPARISON OF COLONOSCOPY AND DOUBLE-CONTRAST BARIUM-ENEMA FOR SURVEILLANCE AFTER POLYPECTOMY

In patients who had undergone colonoscopic polypectomy 1 to 3 years previously, colonoscopy was a more effective method for surveillance than double-contrast Ba-enema. "Available screening methods should make it possible to prevent most deaths from colorectal cancer. All persons 50 years of age and older who are at average risk of colon cancer should undergo comprehensive evaluation of the entire large bowel." "Screening is currently best accomplished by colonoscopy."

6-2 FLAT AND DEPRESSED COLONIC NEOPLASMS: A Prospective Study Of 1000 Colonoscopies In The UK

The polyp-carcinoma hypothesis prompts colonoscopists to search only for polypoid lesions when screening. Many early carcinomas may be missed if flat or depressed neoplasms are not searched for.

6-3 UNFRACTIONATED HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN IN ACUTE CORONARY SYNDROME WITHOUT ST ELEVATION: A Meta-Analysis

In aspirin treated patients with the unstable angina or non-Q-wave infarction (no ST elevation), unfractionated heparin and low-molecular-weight-heparin both reduced risk of myocardial infarction and death by 50%.

There was no evidence of benefit from *long-term* (past 7 days) LMWH.

6-4 MANAGEMENT OF ACUTE CORONARY SYNDROMES

A. High risk patients have all 4 clinical features: Age > 70; Pain at rest; Acute ST *depression* on initial ECG; Elevated troponins

B. Medium risk: One or more of the above; Previous aspirin use; Recurrent ischemia; Previous MI or heart failure;

Post myocardial infarction ischemia; Diabetes

Treatment:

High risk and medium risk patients should receive as routine treatment: aspirin, nitrates, beta-blockers, low molecular weight heparin, statins, and ACE inhibitors. In addition, high risk and most medium risk should receive glycoprotein IIb/IIIa inhibitors given as soon as possible.

6-5 PREVENTING DOG BITES IN CHILDREN: Randomised Controlled Trial Of An Educational Intervention

A brief training period for primary school children increased their precautionary behavior around a dog. A practical application of proper parenting.

6-6 INHIBITORS OF HYDROXYMETHYLGLUTARYL-COENZYME A REDUCTASE AND RISK OF FRACTURE AMONG OLDER WOMEN.

Statin drugs seemed to be protective against non-pathological fractures among older women.

6-7 ORAL STATINS AND INCREASED BONE-MINERAL DENSITY IN POSTMENOPAUSAL WOMEN.

Bone mineral density remained significantly higher in the statin users after adjustment for age, height, and weight.

6-8 WORKING OFF BACK PAIN

Patients, health care workers, and employers should be aware that neither sick leave nor inactivity with bed rest benefits recovery.

Patients should be informed of the generally good prognosis of non-specific back pain and that the worst part of an episode will resolve, in most cases, within a couple of weeks.

6-9 THE INFORMATIONIST: A NEW HEALTH PROFESSION?

The editorialist suggests development of a program, modeled on the experience of clinical librarianship, to train, credential, and pay for the services of information specialists. These new professionals might be called "informationists". Informationists must have a clear and solid understanding of both information science and the essentials of clinical work. They must learn the practical working skills of retrieving, synthesizing, and presenting medical information and the skills of functioning in a clinical care team.

6-10 PROSPECTIVE AUDIT OF INCIDENCE OF PROGNOSTICALLY IMPORTANT MYOCARDIAL DAMAGE IN PATIENTS DISCHARGED FROM EMERGENCY DEPARTMENT.

One out of every 16 patients with acute chest pain discharged from the ED had important myocardial damage. Follow-up measurements with cardiac troponins over the next 24-48 hours is important.

6-11 THE CAUSES AND RISK OF STROKE IN PATIENTS WITH INTERNAL-CAROTID-ARTERY STENOSIS

The risk of stroke among patients with *asymptomatic* stenosis is relatively low. The benefit of endarterectomy should be calculated on the basis of prevention of large-artery strokes. About half of strokes in the territory of an *asymptomatic* stenosis in the internal carotid were not related to the stenosis.

Endarterectomy cannot prevent cardioembolic or lacunar strokes.

"The scales are tipped against the routine use of endarterectomy in patients who have no symptoms."

6-12 SUICIDAL BEHAVIOR IN GAY, LESBIAN, AND BISEXUAL YOUTH

Youths who feel that they are gay must either hide their feelings from others for many years or face the risks of "coming out". Either course is perilous. For some, one consequence of the confusion over their identity in a climate of intense intolerance and victimization may be suicidal behavior.

Epidemiologic studies in North America, and New Zealand show that gay and bisexual males are at least four times as likely to report a serious suicide attempt.

6-13 QUANTITATIVE TESTS FOR HUMAN PAPILLOMAVIRUS

Squamous-cell carcinoma of the cervix is thought to arise from squamous intraepithelial lesions (**SIL**). The degree of thickness of the epithelial changes reflects the relative potential for development of invasive carcinoma.

Human papilloma virus (**HPV**) is strongly associated with cervical cancer. HPV16 is often the associated strain. The prevalence of latent HPV infection is about 40%; 5-10% of these patients will develop SIL; and 1% or less will develop cancer.

6-14 MALARIA CHEMOPROPHYLAXIS WITH TAFENOQUINE: A Randomised Study

Tafenoquine is a new synthetic analogue of primaquine, with an improved therapeutic index and safety profile. It is many times more potent than primaquine against both liver and blood stages of the parasite. It has a much longer half-life than primaquine (14 days vs 6 hours).

Tafenoquine was effective and well tolerated in the prophylaxis of malaria.

6-15 THE RISK OF THE HEMOLYTIC-UREMIC SYNDROME AFTER ANTIBIOTIC TREATMENT OF *ESCHERICHIA COLI* 0157:H7 INFECTIONS

Antibiotic treatment of children with *E coli* O157-H7 increased risk of the hemolytic-uremic syndrome by releasing Shiga toxin from the enteric pathogens. The toxin is absorbed, causing the syndrome.

6-16 THE IMPORTANCE OF DIAGNOSING POLYCYSTIC OVARY SYNDROME

"Diagnosis is extremely important because it identifies risk of potential metabolic and cardiovascular diseases." Reduction in insulin resistance should be a mainstay of any long-term strategy — exercise, diet, and insulin-sensitizing agents (eg, metformin) have been shown to improve risk factors. Low-dose oral contraceptives can be used to treat the characteristic menstrual irregularity and are known to reduce risk for endometrial as well as ovarian cancer.

6-17 THE LANGUAGE OF MEDICATION-TAKING

The editorialist argues that the terms "compliance" and "adherence" are problematic. They exaggerate the physician's control over the process of taking medications and imply that the patient must take the medication as prescribed to obtain benefit. The terms "non-compliance" and "non-adherence" create a clinically unjustifiable distinction between persons who take all of their pills as prescribed and those who deviate from the prescription in any way.

The terms are problematic because they imply that the physician developed the therapeutic plan unilaterally rather than through two-way negotiation with the patient. "Patients base decisions about taking medications on many considerations besides their physician's advice." "Our role is limited to education and advice."

6-18 UPDATE ON ANTIPLATELET THERAPY FOR STROKE PREVENTION

The European Stroke Prevention Study evaluated antiplatelet drugs in *secondary* prevention in over 6500 patients. Aspirin alone reduced risk of second stroke by 18%; extended release dipyridamole alone by 16%; the combination by 37%

6-19 PHYSICAL ACTIVITY AND RISK OF STROKE IN WOMEN

Increasing physical activity levels were associated with substantial reductions in risk for total stroke and ischemic stroke in women. "We observed comparable magnitudes of risk reduction with similar energy expenditure from walking and vigorous activity."

6-20 THE ALCOHOL HANGOVER

Hangover has substantial economic consequences—decreased productivity, absenteeism, poor job performance. "The *primary morbidity* that affects the light-to-moderate drinkers is the hangover, not the long-term consequences of alcohol abuse." "Chronic alcoholism is responsible for only a small proportion of the total societal cost of alcohol use." This is because of the alarming prevalence of *veisalgia* --- 25% of college students reported a hangover in the previous week; 29% reported losing school time. "More than 75% of persons who have consumed alcohol report that they have experienced hangover at least once." Fifteen percent experienced hangover at least monthly.

Screening for hangover severity and frequency may be used to augment strategies for early detection of alcohol dependency. Sons of alcoholic patients are at risk of more frequent hangover. Hangover severity has been used as one of the predictive criteria for alcoholism. Depression and other psychological disorders are more common in patients with hangover.

6-21 PHYSICIAN AND PATIENT SPIRITUALITY: PROFESSIONAL BOUNDARIES, COMPETENCY, AND ETHICS

Spirituality pertains to the ultimate meaning and purpose of life. It has clinical relevance. Clinical studies are beginning to clarify how spirituality and religion can contribute to the coping strategies of many patients with severe, chronic, and terminal conditions.

Should the physician discuss spiritual issues with his or her patients?

What are the boundaries between the physician and patient regarding these issues?

What are the professional boundaries between the physician and the chaplain?

6-22 HEALTH ADVICE AND IMMUNIZATIONS FOR TRAVELERS.

This reference comments on personal precautions and travel-related illnesses, and immunizations.

6-23 EFFECT OF EXERCISE TRAINING ON LEFT VENTRICULAR FUNCTION AND PERIPHERAL RESISTANCE IN PATIENTS WITH CHRONIC HEART FAILURE

In patients with chronic stable HF, exercise training was associated with a reduction in peripheral resistance and a small, but significant improvement in stroke volume and a reduction in cardiomegaly.

RECOMMENDED READING

6-17 THE LANGUAGE OF MEDICATION-TAKING

**6-21 PHYSICIAN AND PATIENT SPIRITUALITY: PROFESSIONAL BOUNDARIES, COMPETENCY,
AND ETHICS**

REFERENCE ARTICLES

6-4 MANAGEMENT OF ACUTE CORONARY SYNDROMES

6-16 THE IMPORTANCE OF DIAGNOSING POLYCYSTIC OVARY SYNDROME

6-22 HEALTH ADVICE AND IMMUNIZATIONS FOR TRAVELERS.

6-1 A COMPARISON OF COLONOSCOPY AND DOUBLE-CONTRAST BARIUM-ENEMA FOR SURVEILLANCE AFTER POLYPECTOMY

Adenomas are precursors of colo-rectal cancer. It is accepted medical practice to remove adenomatous polyps when they are detected in the colon, to search for additional polyps, and to arrange for long-term follow-up.

Which follow-up surveillance procedure is better after polypectomy — barium enema or colonoscopy?

This study compared the two. (A secondary prevention study.)

Conclusion: Colonoscopy was a more effective surveillance method.

STUDY

1. Followed over 950 patients who at previous colonoscopy had an adenoma removed.
2. Performed over 850 paired colonoscopies and double-contrast barium enemas in 580 patients (majority over age 60).
3. The great majority (81%) of examinations were performed within 3 years of the original polyp removal.
4. The Ba-enema was performed first, followed within a few weeks by colonoscopy performed by a colonoscopist unaware of the results of the Ba-enema.

RESULTS

1. Outcomes 850 paired examinations:

	Any polyp	Adenomas	Adenomas >1 cm
Colonoscopy	45%	28%	3%
Ba-enema	26%	11%	1%
2. Thus only about 40% of adenomas discovered on colonoscopy were discovered on Ba-enema.
3. As suspected, Ba-enema was especially ineffective in identifying small adenomas. The rate of detection by Ba-enema rose as the diameter of the adenoma increased. Nevertheless about half of adenomas over 1 cm were missed by Ba-enema
4. Eleven adenomas were detected on Ba-enema and missed by colonoscopy. Repeat colonoscopy discovered the adenoma.
5. Many of the polyps were mucosal tags or hyperplastic polyps. But over 1/4 of the patients had an adenoma.

DISCUSSION

1. Colonoscopy discovered many more polyps than Ba-enema; about half were adenomas.
2. Only about 3% of adenomas discovered by colonoscopy were over 1 cm on this second examination (1 to 3 years after an original adenoma had been removed). This is understandable, given the current knowledge of the slow rate of progression from adenoma to carcinoma. The best estimate of the average time it takes for a new adenoma to grow and transform to cancer is 10 to 20 years.
3. Is combining the 2 procedures beneficial? Only 11 patients had an adenoma uncovered by Ba-enema and missed by colonoscopy. But most will be small.
4. Undoubtedly colonoscopy will miss adenomas, in up to 15 to 20% of examinations. The colonoscopy may not get to the cecum; the rate of complete colonoscopy ranges from 80% to 95%.
5. "Colonoscopic examination has become the preferred way of examining the colon for both detection and removal of polyps, replacing barium enema as a means of surveillance." The lower rate of detection of adenomas over 1 cm is a drawback to Ba- enema."

CONCLUSION

In patients who had undergone colonoscopic polypectomy 1 to 3 years previously, colonoscopy was a more effective method for surveillance than double-contrast Ba-enema.

NEJM June 15, 2000; 342: 1766-72 Original investigation by the National Polyp Surveillance Study Work Group, first author Sidney J Winawer, Memorial Sloan-Kettering Cancer Center, New York

<http://nejm.com>

Comment:

An accompanying editorial (pp 1823-24) comments on a recent British study which found a high prevalence of flat adenomas discovered on the basis of presence of erythema of irregular mucosal folds, enhanced by spraying the mucosa with a dye. These flat adenomas would be much less likely to be discovered by Ba-enema.

See also:

"Use of Colonoscopy to Screen Asymptomatic Adults for Colorectal Cancer" NEJM July 20, 2000; 343: 162-68

<http://nejm.com>

Colonoscopic screening can detect advanced colorectal neoplasms (adenomas > 10 mm in diameter, villous adenomas, and adenomas with high grade dysplasia, or invasive cancer) in asymptomatic adults. Many of these neoplasms would not be detected by sigmoidoscopy. Of the patients with no polyps in the distal colon, 3% had advanced proximal neoplasms.

"Risk of Advanced Proximal Neoplasms in Asymptomatic Adults According to the Distal Colorectal Findings"

NEJM July 20, 2000; 343: 169-74 <http://nejm.com>

Asymptomatic persons over age 50 who had polyps in the distal colon were more likely to have advanced proximal neoplasms than persons without distal polyps. However, if colonoscopic screening is performed only in patients with distal polyps, about half of the cases of advanced proximal neoplasms will not be detected.

<http://nejm.com>

Available screening methods should make it possible to prevent most deaths from colorectal cancer. All persons 50 years of age and older who are at average risk of colon cancer should undergo comprehensive evaluation of the entire large bowel.” “In my judgement, such screening is currently best accomplished by colonoscopy.”

6-2 FLAT AND DEPRESSED COLONIC NEOPLASMS: A Prospective Study Of 1000 Colonoscopies In The UK

Japanese workers have reported the existence of flat and depressed colo-rectal tumors for the past 20 years. They report that up to 40% of adenomas or early colo-rectal carcinomas appear flat, or depressed, rather than as polyps. Outside Japan there have been few reports of such lesions. They have been considered rare in Western countries.

If flat or depressed neoplasms are more common than previously thought, it would have important implications for colo-rectal cancer prevention programs. These lesions are more difficult to detect.

This prospective study determined the prevalence and distributions of flat or depressed neoplasms in the UK using methods developed in Japan.

Conclusion: Flat and depressed colo-rectal neoplasms were common.

STUDY

1. Prospective study performed 1000 consecutive colonoscopies. Patients (mean age 59) were referred for a variety of reasons similar to referrals in the UK. The great majority had some GI symptom or other indication. Only 16% were referred for routine surveillance. (Ie, this was not a screening study of asymptomatic patients.)
2. The colonoscopist looked especially for flat and depressed neoplasms which usually appear as patches of erythema or irregularity of a mucosal fold. As in Japan, dye (indigo carmine) was sprayed directly over suspicious lesions. This made the size and shape of the neoplasm clearly visible.
3. Flat adenomas were defined as mucosal elevations with a flat or slightly rounded surface and a height of less than half the diameter of the lesion. (Most were less than 2 mm in height.) An injection of saline lifted the lesion, permitting more complete resection.

RESULTS

1. In the 1000 patients examined, a total of 321 adenomas were found (32%):
2. Of these, 202 (63%) were polypoid; 117 (36%) were flat. Four appeared depressed.
3. Most of the 321 adenomas contained areas of mild to moderate dysplasia. Ten percent (n = 31) were severely dysplastic. “Lesions containing areas of severe dysplasia (as well as Dukes’ A carcinoma) may be regarded as early cancers and failure to detect and treat these lesions is likely to lead to advanced colorectal carcinoma.”

4. Altogether, there were 37 such lesions – 31 severely dysplastic adenomas and 6 Dukes' A carcinoma. Of 6 Dukes' A carcinomas, 2 were flat, 2 depressed.
5. The overall risk of a flat lesion containing early cancer was greater than that of a polypoid lesion. (14% vs 8%); 54% of lesions containing severe dysplasia or Dukes' A carcinoma were flat or depressed.

DISCUSSION

1. Although two thirds of colo-rectal cancers might develop from adenomatous polyps, they can also develop de novo from normal mucosa.
2. Some carcinomas may have especially aggressive growth patterns, quickly destroying neighboring adenomatous tissue. Flat neoplasms may be more aggressive. Some authorities have reported flat lesions were 10 times more likely than polypoid lesions to contain high grade dysplasia. Indeed, they may represent a variant of the familial adenomatous polyposis.
3. This study confirms the presence of flat and depressed neoplasms in the UK. "Our data suggest that the risk of cancer in flat adenomas was similar to that of protruded lesions when the lesions were smaller than 10 mm in diameter. However, large flat lesions were almost twice as likely as protruded lesions of similar size, to contain areas of severe dysplasia, or foci of invasive carcinoma."
4. "The recognition that colo-rectal cancer can appear flat or depressed has important implications." Unless the colonoscopist focuses on the possibility of these lesions, they may be missed. This may be the reason removal of all polyps failed to prevent up to 24% of all subsequent carcinomas (National Polyp Study).

CONCLUSION

The polyp-carcinoma hypothesis prompts colonoscopists to search only for polypoid lesions when screening. Many early carcinomas may be missed if flat or depressed neoplasms are not searched for.

Lancet April 8, 2000; 355: 1211-14 Original investigation, first author B J Rembacken, General Infirmary, Leeds, <http://www.thelancet.com>

Comment:

This is likely to lead to a major advance in colo-rectal screening. RTJ

6-3 UNFRACTIONATED HEPARIN AND LOW-MOLECULAR-WEIGHT HEPARIN IN ACUTE CORONARY SYNDROME WITHOUT ST ELEVATION: A Meta-Analysis

Both unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) have been widely used in the management of unstable angina and non-Q wave myocardial infarction.

The goal of antithrombotic therapy in these syndromes is to prevent progression of the thrombus and promote stabilization of the atherosclerotic plaque. Aspirin remains the mainstay of therapy. However, despite aspirin, risk of recurrent ischemia remains high (5% to 10% in the first week), and 40% at 6 months.

Does heparin added to aspirin increase benefits? Is one type of heparin more beneficial than the other? How long should heparin be continued? Does long-term heparin improve prognosis?

Aspirin incompletely blocks platelet activation. Heparin inhibits thrombin generation and blocks thrombin activity.

This systematic overview of randomized trials assessed the effect of UFH compared with placebo, and LMWH compared with placebo, and short-term LMWH compared with short-term UFH, for both short- and long-term management.

Conclusion: In patients with unstable angina and non-Q wave infarction, both UFH and LMWH added to aspirin, reduced mortality by about half compared with aspirin alone.

Long-term LMWH added no benefit to aspirin alone.

STUDY

1. Reviewed 12 randomized trials (17 000 patients) with unstable angina or non-Q-wave MI comparing:
 - 1) UFH vs placebo, 2) LMWH vs placebo, 3) Short-term LMWH vs UFH, 4) long-term LMWH vs placebo.
2. All were also taking aspirin.
3. End-point = myocardial infarction or death.

RESULTS

1. Short term (7 days)
 - A. Both UFH and LMWH reduced the end point by about half. (Odds ratio = 0.53; 45 per 1000 vs 74 per 1000). Difference = 29 MIs or deaths per 1000 treated. [NNT(benefit-7 days) = 33]
 - B. For LMWH compared with UFH, the odds ratio was 0.88. (Difference not statistically significant.).
2. Long-term (up to 3 months):

LMWH compared with aspirin alone — odds ratio = 0.98. (No benefit after the first week.).

LMWH long-term was associated with a significantly increased risk of major bleeding (1 per 100 treated.)

DISCUSSION

1. In patients with unstable angina and non-Q wave infarction, addition of UFH or LMWH to aspirin for 7 days reduced incidence of death or MI by about 50%. About 30 major events were prevented for each 1000 patients treated.
2. There was no clear difference between UFH and LMWH in terms of efficacy or safety during short-term therapy.
3. LMWH continued beyond 7 days conferred no additional benefit and resulted in about 10 major bleeding events per 1000 treated.

CONCLUSION

In aspirin treated patients with the unstable angina or non-Q-wave infarction (no ST elevation), unfractionated heparin and low-molecular-weight-heparin both reduced risk of myocardial infarction and death by 50%.

There was no evidence of benefit from *long-term* (past 7 days) LMWH.

Lancet June 3, 2000; 355: 1936-42 Original Investigation, first author John W Eikelboom, McMaster University, Hamilton, Ontario, Canada.

<http://www.thelancet.com>

Comment:

I believe the benefit tilts toward LMWH. It is easier to administer. The point benefit favored it over UFH although there was no significant difference. Other large studies have found outcomes favored LMWH, especially in high-risk patients. See "The TIMI Risk Score for Unstable Angina/Non-ST Elevation MI" JAMA August 16, 2000; 284: 835-42

For a reference article on "Acute Coronary Syndromes" see the following. RTJ

REFERENCE ARTICLE

6-4 MANAGEMENT OF ACUTE CORONARY SYNDROMES

The acute coronary syndrome (ACS) consists of 2 groups: 1) unstable angina and 2) myocardial infarction (MI):

- 1) *Unstable angina* is defined as ischemic-type chest pain of recent origin which is more frequent, severe, or prolonged than the patient's usual angina; is more difficult to control with drugs; or is occurring at rest or minimal exertion. Cardiac enzymes are *not* raised.
- 2) *Myocardial infarction* is defined as ischemic symptoms with raised cardiac enzymes to greater than twice normal. Two types – both with elevation of cardiac enzymes to above twice normal.
 - a. Non-Q-wave myocardial infarction presents similarly to unstable angina. It is an actual infarction without subsequent development of new Q-waves.
 - b. ST elevation myocardial infarction defined as ST elevation on the presenting ECG.

This review considers only unstable angina and non-Q-wave infarction. They are major causes of morbidity and mortality. The initial lesion is erosion or rupture of the fibrous cap of an atherosclerotic plaque leading to an intracoronary thrombus formation. The thrombosis results from platelet activation mediated by exposure of plaque contents. Downstream embolism from a friable coronary thrombus may occur, causing focal cell necrosis and release of cardiac troponins.

Optimal treatment of ST-elevation MI is clearly defined. Management of unstable angina and non-Q-wave infarction remains controversial because of the heterogeneous nature of these conditions and recent advances in treatment options.

This article discusses risk stratification of unstable angina and non-Q-wave MI based on symptoms, the initial ECG, and serum markers:

- A. High risk patients have all 4 clinical features: Age > 70; Pain at rest; Acute ST *depression* on initial ECG; Elevated troponins

B. Medium risk: One or more of the above; Previous aspirin use; Recurrent ischemia; Previous MI or heart failure; Post myocardial infarction ischemia; Diabetes

Treatment:

High risk and medium risk patients should receive as routine treatment: aspirin, nitrates, beta-blockers, low molecular weight heparin, statins, and ACE inhibitors. In addition, high risk and most medium risk should receive glycoprotein IIb/IIIa inhibitors given as soon as possible.

Most will go on to early angiography and intervention.

BMJ July 22, 2000; 321: 220-23 "Clinical Review", first author S J Maynard, Royal Victoria Hospital, Belfast, UK
<http://www.bmj.com/cgi/content/full/321/7255/220>

Several glycoprotein IIb/IIIa antagonists are available:

Tirofiban (*Aggrastat*; Merck) is a non-peptide reversible antagonist of fibrinogen binding to the glycoprotein IIb/IIIa receptor on the platelet surface. It prevents platelet aggregation. It must be given IV. Action is rapid and half life short.

Abciximab (*ReoPro*; Centocor) is an antibody prepared by monoclonal technology. It also binds to the platelet surface glycoprotein IIb/IIIa and prevents platelet aggregation.

The UK National Institute for Clinical Excellence (NICE) recommends treatment with GP IIb/IIIa antagonists for all high risk patients who have had a minor heart attack, unstable angina, or who are undergoing balloon angioplasty. This despite the considerable cost.

6-5 PREVENTING DOG BITES IN CHILDREN: Randomised Controlled Trial Of An Educational Intervention

Dog bites are a major cause of injury, especially in children. There have been no evaluations of interventions designed to teach people how to avoid being attacked by a dog.

"Prevent-a-Bite" is an educational program designed for primary school children. It teaches precautionary behavior around dogs.

This study assesses efficacy of the program in prevention of dog-bites in children.

Conclusion: The program led to precautionary behavior around dogs.

STUDY

1. Randomized, controlled trial entered over 300 children age 7 to 8 in eight different schools.
2. In 4 of the schools children were taught precautionary behaviors. The other 4 were controls.
3. The intervention consisted of a 30 minute lesson conducted by an accredited dog handler who demonstrated "dos" and "don'ts":

How to recognize friendly, angry, or frightened dogs

How to approach a dog they wanted to pat

Asking permission of the owner

Approaching slowly

Extending the hand palm down

Patting the dog under the chin and on the chest

Avoiding eye contact

Walking away slowly and quietly

Precautionary and protective body postures to adopt when approached or knocked down by a dog

Not to disturb a friendly, known dog when it is sleeping, eating, tied up, or in a car.

4. A week after the class, children in both the intervention and the control schools were let out to play unsupervised in the school grounds. A docile Labrador dog was tethered five meters away from its owner who was disguised as a tradesman. The children had been told the dog was there.
5. Videotapes were made to record children's behavior.

RESULTS

1. Children in the intervention group displayed better precautionary behavior. They were circumspect, typically observing the dog from distance. A few patted the dog after a considerable period of careful assessment.
2. Most of the children in the control group patted the dog without hesitation and tried to excite it.

DISCUSSION

1. In the short term, the intervention increased the precautionary behavior of children around a dog. Long-term effects are not known.

CONCLUSION

A brief training period for primary school children increased their precautionary behavior around a dog. A practical application of proper parenting.

BMJ June 3, 2000; 320: 1512-13 Original investigation, first author Simon Chapman, University of Sydney, Australia.

<http://www.bmj.com/cgi/content/full/320/7248/1512>

Comment:

This, of course, is a surrogate end-point. Whether the intervention will prevent dog bites was not determined. It would be reasonable to assume that it would.

Parents can learn how to teach their children safe behavior around dogs. This is good parenting. RTJ

6-6 INHIBITORS OF HYDROXYMETHYLGLUTARYL-COENZYME A REDUCTASE AND RISK OF FRACTURE AMONG OLDER WOMEN.

Statin drugs increase new bone formation in rodents and in human cells in vitro. Statins are also reported to increase bone mineral density of the femoral neck.

This study assessed the effect of statins on risk of fracture in postmenopausal women.

Conclusion: Statins seemed to effectively reduce fracture risk.

STUDY

1. Case-control study entered over 3500 women over age 60.

Cases: Identified non-pathological fracture in over 900 women -- an incident diagnosis of non-pathological fracture of hip, humerus, distal tibia, wrist, and vertebra.

Controls: Matched with over 2700 women without fracture. None were taking drugs to treat osteoporosis.

2. Determined, from pharmacy records, use of statin drugs (5 different) over the previous 2 years.

RESULTS

1. Women with 13 or more records of statin dispensing had a decreased risk of fracture (Odds ratio = 0.48) after adjustment for age, number of hospital admissions, chronic disease score, and use of non-statin lipid-lowering drugs.
2. In absolute terms, the incidence of fracture was 2.5% in statin takers, and 3.1% in controls.
[By my calculation NNT (benefit-2 years)= 166 RTJ]
3. No difference between women taking non-statin lipid-lowering drugs and controls.

DISCUSSION

1. Statins seem to be protective against non-pathological fractures among older women using them regularly over 2 years.
2. This is compatible with the hypothesis that statins increase bone mineral density.
3. The effective minimum dose and duration that confers protection was not determined. At least a year seems likely.

CONCLUSION

Statin drugs seemed to be protective against non-pathological fractures among older women.

Lancet June 24, 2000; 355: 2185-88 Original investigation, first author K Arnold Chan, Channing Laboratory, Brigham and Women's Hospital, Boston.

<http://www.thelancet.com>

See also:

1. "HMG-CoA Reductase Inhibitors and the Risk of Hip Fractures in Elderly Patients" JAMA June 28, 2000; 283: 3211-16 <http://www.jama.com>
2. "HMG-CoA Reductase Inhibitors and the Risk of Fractures" JAMA June 28, 2000; 283: 3205-10 <http://www.jama.com>
3. "Do Statins Prevent Both Cardiovascular Disease and Fracture?" JAMA June 28, 2000; 283: 3255-57 <http://www.jama.com>

Comment:

It is unusual for several similar investigations to appear simultaneously in two major journals. All original investigations came to the same conclusion, supporting a protective association of statins and prevention of osteoporotic fracture.

I believe the evidence is strong enough to tell elderly persons, both men and women, of this added advantage.

How will statins compare with bisphosphonates and estrogens in delaying onset of osteoporosis? Will concomitant use provide any advantage? RTJ

6-7 ORAL STATINS AND INCREASED BONE-MINERAL DENSITY IN POSTMENOPAUSAL WOMEN.

This case-control study investigated the possibility that bone formation would be increased in postmenopausal women taking statin drugs.

Measured bone mineral density (**BMD**) at the spine and hip in 41 women (the cases) taking any one of 6 statin drugs and 100 matched controls. The median length of time taking the statins was 48 months.

BMD remained significantly higher in the statin users after adjustment for age, height, and weight. (eg, adjusted spine BMD = 0.99 g/cm² in cases vs 0.0.91 g/cm² in controls.)

Mechanism of action is unknown.

Lancet June 24, 2000; 355: 2218-19 Original investigation, first author C J Edwards, St Thomas's Hospital London <http://www.thelancet.com>

6-8 WORKING OFF BACK PAIN

About 80% of all people will, at sometime in life, experience back pain. Low back pain is the commonest cause of limited activity among people under age 45, and is one of the commonest reasons for seeking health care. Disability from back pain has increased greatly over the past decades.

In most cases, the cause is unknown, although generally thought to be multifactorial. The natural history is highly variable.

"Back pain cannot be viewed as only a medical disorder, but rather as a biological-psychological-social complex in which the psychological aspects are very common."

Back pain has been associated with personality disorders, such as depressive or anxious types. Preexisting psychological distress has been found to influence incidence of new episodes of back pain. "Prevention of occupational low back pain may be improved by management of psychological distress."

Evidence supports the advice for patients to continue ordinary activities of daily living as normally as possible despite the pain. The longer a patient is off work because of back pain, the greater the risk of chronic pain and the lower the chance of ever returning to work.

Several suggestions:

Patients, health care workers, and employers should be aware that neither sick leave nor inactivity with bed rest benefits recovery.

Patients should be informed of the generally good prognosis of non-specific back pain and that the worst part of an episode will resolve, in most cases, within a couple of weeks.

If pain is not resolved within 1 to 4 months, advice about rehabilitation programs may be given. The program may, for some chronic cases, consist of multidisciplinary interventions.

Lancet June 3, 2000; 355: 1929-30 Editorial by Fin Bering-Sorensen, Copenhagen University Hospital, Denmark.
<http://www.thelancet.com>

Comment:

Many authorities have commented on the need to continue daily activity as much as possible, allowing self-cure of the pain. The message is worth repeating. RTJ

6-9 THE INFORMATIONIST: A NEW HEALTH PROFESSION?

Physicians still do not regularly search the medical literature themselves, nor do they ask for professional help in searching nearly as often as they need to. Many questions arising in clinical encounters that can, and should be answered on the basis of evidence from the published literature are never addressed.

Published evidence is scattered. Electronic indexing of articles is far from ideal. Most physicians now in practice have not acquired the skills of literature retrieval. If the skills acquired are not used regularly, they decay.

Physicians don't and never will have the time to look for the answers to most of their clinical questions themselves. "Complicating the demands for literature retrieval is the need to judge the quality of the retrieved literature and extract the essential information from it, using techniques of critical appraisal. These techniques are not easy to teach and are time-consuming to apply. Once useful information has been dug out of the literature, the task of linking it to the case at hand remains."

"Many opportunities for improved patient care and continued learning are missed. Much of the effort, creativity, and money that go into biomedical research is simply wasted."

Clinical librarians have the ability to read the full text of most pertinent articles, identify and extract the relevant information, write brief synopses of their findings, and present them on rounds and at conferences. But, with few notable exceptions, mostly in large academic centers, clinical librarianship has failed to take root and flourish.

The editorialist suggests development of a program, modeled on the experience of clinical librarianship, to train, credential, and pay for the services of information specialists. These new professionals might be called "informationists". Informationists must have a clear and solid understanding of both information science and the essentials of clinical work. They must learn the practical working skills of retrieving, synthesizing, and presenting medical information and the skills of functioning in a clinical care team.

Clinicians must recognize the importance of informationists, understand their role, and actively include them in the process of care.

Annals Int Med June 20, 2000; 132: 996-98 Editorial by Frank Davidoff, Editor Annals Int Med, and Valarie Florence, Association of Medical Colleges. <http://www.annals.org>

Comment:

I believe services of a complete informationist would be out of the reach of most group primary care practices. It would, however, be possible to assign individuals within the group into subsets according to the information desired. It would not be essential, by any means, to search all the virgin literature. The group informationists can rely on the work of others who have already done this — eg, The *ACP Journal Club*, and the Cochrane Library. And even some abstracting services such as *Practical Pointers*.

However, even after the best information is retrieved, the clinician has the responsibility to tailor the information to the individual patient, taking into account his or her autonomy and preferences, cost and resources available in the community, co-morbidity, and culture. Just obtaining the best information does not automatically lead to the best application. Obtaining and applying the best evidence does not necessarily translate into benefit for the individual. Randomized trials and meta-analyses (considered the best evidence) present quantitative estimates – a number needed to treat over a specified time to benefit one patient. Often a favorable NNT is 10; an exceptional NNT is 3. This means that the treatment over the specified time will not benefit 9 out of 10; nor 2 out of 3. And is associated with expense, inconvenience, and possible harm. RTJ

6-10 PROSPECTIVE AUDIT OF INCIDENCE OF PROGNOSTICALLY IMPORTANT MYOCARDIAL DAMAGE IN PATIENTS DISCHARGED FROM EMERGENCY DEPARTMENT.

Patients presenting to the ED with chest pain of unknown cause are a management challenge. Clinical history and examination are imperfect tools for diagnosis. The admission ECG, although an excellent test for selecting patients for thrombolysis, has a diagnostic sensitivity for acute myocardial infarction (AMI) of 55-75%

"Measurement of cardiac troponins T and I has greatly improved diagnosis for patients presenting with suspected acute coronary syndromes. But, the diagnostic time window of these markers is wide, being up to 72 hours. The markers have 100% sensitivity for diagnosing acute myocardial infarction 12 hours after presentation to hospital,¹ and concentrations remain elevated for as long as 10 days.

Raised concentrations of cardiac troponins are completely cardiac specific, unlike increased concentrations of creatine kinase and its MB isoenzyme.

This study assessed incidence of prognostically important myocardial damage in patients with chest pain who were discharged from the ED after a negative evaluation.

Conclusion: Repeat evaluation discovered that 6% of the patients discharged had important myocardial damage.

STUDY

1. Prospective observational study entered 110 patients presenting to the ED with chest pain of unknown cause. All were discharged home after cardiac causes had been ruled out by clinical evaluation (including normal creatine kinase measurements) and normal ECG.
2. Reviewed 12-48 hours later by repeat ECG and measurement of cardiac troponin T.

RESULTS

1. The patients had no symptoms after discharge. The repeat ECG at 12-48 hours was still normal in all.
2. Seven patients of the 110 (6%) had elevated cardiac troponin T (≥ 0.1 ug/L) indicating

myocardial damage. Four had concentrations > 0.5 ug/L, which has a 95% specificity for non-Q wave infarction.²

3. All seven were referred for further cardiac assessment.

DISCUSSION

1. Raised troponin levels predict risk of subsequent cardiac events. The size of the risk depends on how high the concentration is. "In patients without electrocardiographic changes, a cut-off of 0.1 ug/L is the optimal predictor of death."
2. Data from the U.S. frequently state that, of the 4 million patients presenting annually with chest pain who are sent home after a negative evaluation, about 2 in 1000 have undiagnosed AMI. However, a recent study which measured cardiac troponins showed an incidence of prognostically important myocardial damage in 6 % of patients without a diagnostic ECG on presentation.
3. Some of these patients will have had an AMI; some unstable angina.
4. Missed acute coronary syndromes is a frequent cause of malpractice claims.
5. More importantly, these patients are deprived of the opportunity to enter secondary prevention programs which will improve their survival.

CONCLUSION

Many patients with acute chest pain studied in an ED are discharged without a diagnosis of myocardial ischemia. Of patients presenting with acute chest pain who had negative findings in the ED, about 6% actually had ischemic myocardial damage.

Discharged chest pain patients should be followed for 24-48 hours with repeat cardiac troponins to disclose the few who have undetected ischemic damage.

BMJ June 24, 2000; 320: 1702-05 Original investigation, first author, P O Collinson, St George's Hospital, London UK

<http://www.bmj.com/cgi/content/full/320/7251/1702>

Comment:

- 1 This means that if the patient has an AMI, troponin tests will always be positive within 12 hour (Ie, no false negative tests — no patient with an acute MI will have a troponin below 0.1 at 12 hours.). Is this true? Do none rise after 12 hours? What about testing at 6 hours?
- 2 This means, in patients who do *not* have an Q-wave infarction, 95% have levels below 0.5 ug/L. (95% true negative tests for acute MI.) 5% would have levels > 0.5% (ie, 5% false positive tests). Is this true? Some of these may have unstable angina. (About 30% of patients with unstable angina have raised troponins. The distinction between acute non-Q-wave infarction and unstable angina is blurred.)

Nevertheless, the clinical application is obvious. Patients presenting to ED with acute chest pain who are subsequently discharged after a negative work up require routine follow-up. RTJ

6-11 THE CAUSES AND RISK OF STROKE IN PATIENTS WITH INTERNAL-CAROTID-ARTERY STENOSIS

"Whether to perform carotid endarterectomy in asymptomatic patients is an important issue." Over 70 000 endarterectomies were performed in the US in asymptomatic patients in 1997.

Two million persons in the US over age 50 are estimated to have asymptomatic carotid stenosis of at least 50% of luminal diameter.

Internal carotid atherosclerosis is an important cause of stroke. Endarterectomy does reduce risk of stroke. The benefit rises if symptoms are present, with a greater degree of stenosis, and if the rate of perioperative morbidity and mortality is low. If the perioperative mortality is under 6%, *symptomatic* patients with 70% to 99% stenosis undergoing endarterectomy have an absolute reduction in risk of up to 15% within 5 years. [NNT(benefit - 5 years) = 7]. Benefit is marginal in patients with this degree of stenosis who are *asymptomatic* — about 6% reduction of risk on 5 years [NNT(benefit-5years)=16].

Decisions about carotid surgery in asymptomatic patients must take into account that not all future strokes will originate from the artery. In patients with severe symptomatic stenosis, about 20% of subsequent ipsilateral strokes have a cardiac or lacunar cause. The rate of future stroke due to non-carotid causes may be much higher in patients with asymptomatic stenosis. Thus, any benefit of surgery would be relatively less.

This study assessed the causes, severity, risk, and predictors of stroke in patients with asymptomatic carotid stenosis.

Conclusion: Almost 50% of strokes were attributed to small vessel lacunes or cardioembolism and not due to the carotid lesion.

STUDY

1. Followed over 1800 patients with unilateral *symptomatic* stenosis and contralateral *asymptomatic* stenosis.
2. Risk of a first stroke over 5 years was compared in the symptomatic side with the asymptomatic side:

	Asymptomatic side (%)	Symptomatic side(%)
No disease	5	
<50% stenosis	8	19
50-59% 13		20
60-74% 15		26
75-94% 19		27
95-99% 15		17
Occlusion	9%	

(Note the decline in risk as near-occlusion is reached. RTJ)

3. Thus, risk increased with the severity of the stenosis in both groups.
 4. Risk of stroke (%):
- | | Cardioembolic | Lacunar | Larger-artery |
|---------------|---------------|---------|---------------|
| <60% stenosis | 1.2 | 1.9 | 6.4 |
| 60-99% | 2.1 | 6.0 | 9.9 |

(Thus in both groups, cardioembolic and lacunar causes accounted for almost half the strokes.)

DISCUSSION

1. Almost half the strokes in the territory of an asymptomatic carotid artery in patients with 60 to 99% stenosis were attributable to lacunar or cardioembolic disease. Thus, endarterectomy to prevent future stroke is not as beneficial as might be assumed.
2. "Our data suggest that endarterectomy may not be justified for most patients with *asymptomatic* carotid-artery stenosis" Depending on the risk of surgery, endarterectomy might cause more mortality and morbidity than it would prevent.
3. This differs from the recommendations of the American Heart Association whose guidelines include a "Grade A recommendation" for the use of endarterectomy in asymptomatic patients with 60% to 99% stenosis, provided the rate of perioperative stroke and death is less than 3% and life expectancy is at least 5 years. At the time of the recommendations, information about stroke due to specific causes was not available.
4. Indeed, the benefit of surgery in patients with *symptomatic* stenosis may not be impressive. Another large study reported an absolute difference in risk over 5 years of 7% among symptomatic patients with 60 to 69% stenosis. "It seems paradoxical to recommend endarterectomy for *asymptomatic* patients with 60 to 69 percent stenosis on the basis of a projected clinically important benefit, when for *symptomatic* patients with the same degree of stenosis, as well as a much greater risk of subsequent stroke, the benefit was small."

CONCLUSION

The risk of stroke among patients with asymptomatic stenosis is relatively low. The benefit of endarterectomy should be calculated on the basis of prevention of large-artery strokes. About half of strokes in the territory of an asymptomatic stenosis in the internal carotid were not related to the stenosis.

Endarterectomy cannot prevent cardioembolic or lacunar strokes.

"The scales are tipped against the routine use of endarterectomy in patients who have no symptoms."

NEJM June 8, 2000; 342: 1693-700 Original investigation by the North American Carotid Endarterectomy Trial Collaborators, first author Domenico Inzitari, University of Florence, Italy

<http://www.nejm.com>

An editorial in this issue of NEJM (pp 1744-45) disagrees somewhat. The decision for endarterectomy in patients should be based on the hemodynamic importance of the carotid lesion and the risk of surgery to the individual patient, rather than a uniform policy of using medical therapy for all asymptomatic patients.

The editorialists point out that stenosis of 70% or more (ie to 1.5 mm) represents the point at which a pressure drop across the stenosis occurs in most persons — ie, the point where it becomes hemodynamically important. If collateral flow is not adequate, low flow transient ischemic attacks and infarcts develop. Even if there is good collateral circulation, reduced flow in the affected artery may promote formation of thrombi which embolize or propagate distally to cause sudden stroke.

Comment:

There must be asymptomatic patients for whom endarterectomy is highly likely to prevent stroke. How should we recognize and advise them? A higher degree of stenosis should be present.

The patient should be symptomatic and not be aged and infirm — co-morbidity low, and controlled (eg diabetes, hypertension). Surgery should be in good hands with a proven track record. The patient should state a preference after being informed as accurately as possible about risks and benefits. RTJ

6-12 SUICIDAL BEHAVIOR IN GAY, LESBIAN, AND BISEXUAL YOUTH

Sexual orientation emerges strongly during adolescence. Youths with emerging identities that are gay, lesbian, or bisexual, living in generally hostile climates, face particular dilemmas. They are well aware that in many secondary schools, the words "fag" and "dyke" are terms of denigration and that anyone who is openly gay, lesbian, or bisexual faces social exclusion and psychological and physical persecution.

Some of their families too will express negative feelings. Youths in such families may be victimized if they disclose that they are not heterosexual.

Youths who feel that they are gay must either hide their feelings from others for many years or face the risks of "coming out". Either course is perilous. For some, one consequence of the confusion over their identity in a climate of intense intolerance and victimization may be suicidal behavior.

Epidemiologic studies in North America, and New Zealand show that gay and bisexual males are at least four times as likely to report a serious suicide attempt.

In the U.S., more youths are disclosing their gay, lesbian, or bisexual orientation during high school, especially as more support services are being made available. However, homophobia persists. Many families remain unable to respond positively to their gay, lesbian and bisexual children and have little access to information and support. This in turn may contribute to the stresses in adolescents' lives — stresses that can lead to despair.

This is an international problem that is associated with homophobic legislation.

BMJ June 17, 2000; 320: 1617-18 Editorial by Christopher Bagley, University of Southampton, UK and Anthony R D'Augelli, Pennsylvania State University, University Park, USA

<http://www.bmj.com/cgi/content/full/320/7250/1617>

6-13 QUANTITATIVE TESTS FOR HUMAN PAPILLOMAVIRUS

Squamous-cell carcinoma of the cervix is thought to arise from squamous intraepithelial lesions (**SIL**). The degree of thickness of the epithelial changes reflects the relative potential for development of invasive carcinoma.

Human papilloma virus (**HPV**) is strongly associated with cervical cancer. HPV16 is often the associated strain. The prevalence of latent HPV infection is about 40%; 5-10% of these patients will develop SIL; and 1% or less will develop cancer.

Two articles in this issue of Lancet^{1,2} add information. A high virus load over many years increases the risk of developing carcinoma in situ (CIS) many years (up to 19) later. Women with *persistently* high viral loads have the greatest risk. Of women under age 25 who have a persistently high viral load, 25% will develop CIS.

The average time between detection of HPV and CIS was 8 years, although shorter time periods have been reported. CIS is a slowly developing disease.

Quantitation of viral load might be added to cytology to reduce the number of women referred for treatment of mildly abnormal Pap smears. The viral load of HPV16 may be used to identify women with normal or mildly abnormal smears who are at high risk. And possibly candidates for chemoprophylaxis.

Lancet June 24, 2000; 35: 2179-80 Editorial by Carolyn Johnston, University of Michigan Hospital, Ann Arbor.
<http://www.thelancet.com>

1 "Viral Load Of Human Papilloma Virus 16 As A Determinant For Development Of Cervical Carcinoma In Situ."
Lancet June 24, 2000; 355: 2189-93

Analysis of the amount of HPV DNA can predict cancer risk at a stage when current screening methods are uninformative. Women in the highest quintile concentrations of HPV16 DNA were at a 60-fold higher risk of developing CIS. The first Pap smear samples in these women are often classified as normal.

2 "Consistent High Viral Load Of Human Papillomavirus 16 And Risk Of Cervical Carcinoma In Situ."

Lancet June 24, 2000; 355: 2194-98

Risk is high in those women with high viral loads identified by a quantitative HPV test. Women at high risk could be identified by a quantitative test in addition to a Pap smear.

Comment:

Will this be a marker similar to adenoma of the colon as related to cancer of the colon? Risk may be identified years before development of CIS.

Infection may wax and wane over time, depending on immune response. Does this predict an effective vaccine or antiviral therapy? Immunocompromised patients will have rapid progression of the infection and much higher risk.

Tonsillar carcinoma is also reported to be related to HPV infection. RTJ

6-14 MALARIA CHEMOPROPHYLAXIS WITH TAFENOQUINE: A Randomised Study

Currently, malaria prophylaxis relies on a few drugs. Mefloquine, doxycycline, and chloroquine/proguanil are the most widely used. Each has disadvantages. Regimens in which daily intake is necessary are associated with low compliance among short-term visitors to endemic areas and limit the possibility of mass treatment during epidemics.

Primaquine is active against the liver stages of Plasmodium species. This makes it useful for prophylaxis against *P falciparum* because it eliminates the need for continued intake after exposure to malaria ends (in contrast to drugs active only against the blood stages). General use has been restricted because of gastrointestinal side-effects and a short half-life. Daily dosing is needed.

Tafenoquine is a new synthetic analogue of primaquine, with an improved therapeutic index and safety profile. It is many times more potent than primaquine against both liver and blood stages of the parasite. It has a much longer half-life than primaquine (14 days vs 6 hours).

This study assessed efficacy and safety of tafenoquine in different doses.

Conclusion: Tafenoquine was effective and safe.

STUDY

1. Randomized, double-blind study assigned over 400 subjects in Gabon, and endemic area, to:
 - 1) Tafenoquine (4 different doses; 250, 125, 62.5, and 31.25 mg), or 2) placebo daily for 3 days.
2. Almost all had received initial curative treatment with halofantrine daily for 3 days before start of tafenoquine.
3. Follow-up 70 days with weekly thick smears.

RESULTS

1. At day 77 positive smears were recorded in 14/82 of the placebo group. And *none* of 84 who had received 250 mg of tafenoquine daily for 3 days.
2. Doses lower than 250 mg afforded significant, but not complete protection.
3. Numbers of adverse events did not differ significantly between tafenoquine and placebo..

DISCUSSION

1. Tafenoquine was safe and effective. The duration of protection was long due to its long half life and its efficacy against hepatic stages of the parasite.
2. A 3-day course of 250 mg seems a reasonable dose.
3. "If the desired duration of protection is a few weeks, as in the case for non-immune individuals in epidemics, or during short term visits to a malarial area, tafenoquine has the potential to replace other regimens as the drug of choice."
4. Tafenoquine is also effective against other plasmodia species.
5. Possible rare adverse effects cannot be ruled out by this study.

CONCLUSION

Tafenoquine was effective and well tolerated in the prophylaxis of malaria.

Lancet June 10, 2000; 355: 2041-45 Original investigation, first author Bertrand Lell, Albert Schweitzer Hospital, Lambarene, Gabon. <http://www.thelancet.com>

E coli O157:H7 causes sporadic and epidemic GI infections worldwide. About 15% of children in North America infected with O157:H7 develop the hemolytic-uremic syndrome (**HUS**) soon after onset of the diarrhea.

HUS is characterized by thrombocytopenia, hemolytic anemia, and nephropathy. It is believed to be caused by Shiga toxins elaborated by O157:H7 and other *E coli*. Various antibiotics cause *E coli* in the bowel to release Shiga toxin, making the toxin more available for absorption.

"Treatment with antibiotics does not ameliorate *E coli* O157:H7 infections and in some studies has been associated with worse clinical outcomes."

This study determined whether antibiotic treatment alters the risk of HUS among children infected with *E coli* O157:H7.

Conclusion: Antibiotic treatment increased risk of HUS in this group of children.

Study

1. Prospective cohort study entered 71 children younger than age 10. All had diarrhea caused by O157:H7.
2. Nine of 71 (13%) received antibiotics.

Results

1. Of the 71 children, 10 (14%) developed HUS:
2. Of the 10, 5 had received antibiotics (2 trimethoprim-sulfamethoxazole; 3 cephalosporins); 5 had not.
3. Thus, 5 of 9 (55%) who received antibiotics developed HUS vs 5 of 62 (8%) of those who did not receive antibiotics. Four of the 10 required dialysis; 7 required erythrocyte transfusions, platelet transfusions, or both.
4. Those with an initial white blood count above 11 000 were much more likely to develop HUS.

DISCUSSION

1. Sulfa-containing antibiotics and beta-lactams were associated with a similar degree of risk.
2. "Despite the absence of an association between treatment with antimotility drugs and opioid narcotics and the risk of hemolytic-uremic syndrome, we recommend *against* the use of these drugs in children with acute diarrhea, because of their association with complications of O157:H7 and with the prolongation of symptoms." ¹
3. "We recommend against giving antibiotics to children who may be infected with *E coli* O157:H7 until the results of a stool culture indicate that the pathogen responsible is one that is appropriately treated by an antibiotic. Even if the small advantage associated with empirical fluoroquinolone therapy in some adults with acute diarrhea holds true for children, we believe the risk of administering antibiotics to children who might be infected with pathogens for which antibiotics are contraindicated, (ie, *E coli* O157:H7) exceeds the potential benefit." ¹
4. It is important to remember that the HUS can occur in children who have not received antibiotics.

CONCLUSION

Antibiotic treatment of children with *E coli* O157-H7 increased risk of the hemolytic-uremic syndrome.

NEJM June 29, 2000: 342: 1930-36 Original investigation, first author Craig S Wong, University of Washington School of Medicine, Seattle <http://www.nejm.com>

Comment:

1 If no antibiotics are given, and no symptomatic therapy in the form of antimotility drugs is indicated, only bismuth compounds (*Pepto-Bismol*) and supportive therapy with fluids remain. I doubt that adults who develop "traveler's diarrhea" will accept this. I believe most will demand antibiotics.

See the review article this month in Practical Pointers (6-22) on advice to travelers for self treatment of acute traveler's diarrhea:

A. Non-dysenteric diarrhea:

a. Fluid replacement

b. Loperamide (*Imodium*; generic) with or without an antimicrobial agent.

Do not use for children under age 2. Do not use antimotility agents *alone* if either fever or blood in stool is present. Some experts would not use any antimotility drug at all if diarrhea was associated fever or blood in stool

c. Antimicrobial agent. Eg, a single dose of ciprofloxacin (*Cipro* - 750 mg) or levofloxacin (*Levaquin* - 500 mg) or, azithromycin (*Zithromax* - 500 mg)

d. Bismuth subsalicylate (*Pepto-Bismol* -- 2 tablets or 2 tablespoons 4 times daily) has been used for prophylaxis

B. Severe or dysenteric diarrhea:

a. Antimicrobial agent – eg, ciprofloxacin (500 mg twice daily for 3 days); levofloxacin (500 mg once daily for 3 days, or azithromycin (500 mg once on day one then 250 mg daily for 4 days, or 1000 mg once only.)

REFERENCE ARTICLE

6-16 THE IMPORTANCE OF DIAGNOSING POLYCYSTIC OVARY SYNDROME

Most women with hyperandrogenism show evidence of a disorder known as the polycystic ovary syndrome. (PCOS)¹ The syndrome is ". . .extremely common, but heterogeneous". It ". . .is considered the most frequently encountered endocrinopathic condition".

Originally the diagnosis required pathognomonic ovarian findings and the clinical triad of hirsutism, amenorrhea, and obesity. Later, abnormalities of the hypothalamic-pituitary axis were noted, focusing the diagnosis on endocrine criteria such as elevations of serum luteinizing hormone and increased luteinizing hormone/ follicle-stimulating-hormone ratio.

Most women with PCOS have some degree of insulin resistance, although it may be subtle.

A characteristic polycystic ovary can be recognized by ultrasound. However, polycystic ovaries can occur in some "normal" women, as well as other conditions. Polycystic ovaries, by themselves, do not make the diagnosis. This ignores the typical endocrine features which are a requirement for the diagnosis. "Hyperandrogenism and chronic anovulation remain the two most characteristic features of the disease."

PCOS is associated with infertility, abnormal bleeding, increased pregnancy loss, and complications of pregnancy. Because of long-standing estrogen stimulation, there is an increased risk of endometrial cancer.

The article goes on to describe features of hyperandrogenism (elevated serum testosterone is the best marker), anovulation, ultrasound, insulin resistance and impaired glucose tolerance and diabetes, altered lipid profiles (eg, low HDL-cholesterol), obesity, and related cardiovascular disease.

"Diagnosis is extremely important because it identifies risk of potential metabolic and cardiovascular diseases." Reduction in insulin resistance should be a mainstay of any long-term strategy — exercise, diet, and insulin-sensitizing agents (eg, metformin) have been shown to improve risk factors. Low-dose oral contraceptives can be used to treat the characteristic menstrual irregularity and are known to reduce risk for endometrial as well as ovarian cancer.

Annals Int Med June 20, 2000; 132: 989-93 "Perspective". review article by Rogerio A Lobo and Enrico Carmina, Columbia University College of Physicians and Surgeons, New York. <http://www.annals.org>

1 Originally described in 1935 and called the Stein-Leventhal syndrome.

RECOMMENDED READING

6-17 THE LANGUAGE OF MEDICATION-TAKING

"Hundreds of studies have found that only 50% to 60% of patients consume their medications for chronic diseases as prescribed." Intensive interventions only marginally improve medication-taking or therapeutic outcomes.

"Reassessment of an issue as basic as the language we use to describe it may be necessary to identify new strategies for clinical intervention."

The terms "compliance" and "adherence" are problematic. They exaggerate the physician's control over the process of taking medications and imply that the patient must take the medication as prescribed to obtain benefit. The terms "non-compliance" and "non-adherence" create a clinically unjustifiable distinction between persons who take all of their pills as prescribed and those who deviate from the prescription in any way.

The terms are problematic because they imply that the physician developed the therapeutic plan unilaterally rather than through two-way negotiation with the patient. "Patients base decisions about taking medications on many considerations besides their physician's advice." "Our role is limited to education and advice."

The terms also suggest that conformity to our instructions for medication-taking is necessary to obtain the goals of therapy. "The history of drug development is replete with reminders that our prescriptions themselves may change as evidence accumulates about the optimal dose of duration of treatment."

Terms such as non-compliant and non-adherent blur important distinctions between different patient behaviors. Patients who do not fill their prescriptions (at times due to an unrecognized cost barrier) differ from those who miss an occasional pill, take a consistent but reduced dose, consume medication sporadically, or completely discontinue use. Indeed, a strategy of "intelligent noncompliance" has been described in which patients accurately conclude that they can attain the treatment goal by unilaterally reducing their medication dose. For example, many patients with hypertension attain blood pressure control despite taking less medication than prescribed. "Because we may not know what proportion of the medication dose must be taken to achieve a desired therapeutic outcome, we should be reluctant to use a term that stigmatizes patients who do not consume every pill." "In such circumstances the clinician's treatment recommendation rather than the patient's behavior should be changed."

"Patients with chronic health conditions express concerns about dependence on physicians and medications and often experiment medication doses to restore their sense of self-control." Patients also incorporate suggestions from family members, acquaintances, and the media. "In other words, patients view the physician's prescription as a clinical guideline rather than a treatment standard."

Language is an important component of our pharmacopoeia. Words make a difference. The terms compliance and adherence should be abandoned. They subtly exaggerate the importance of the clinician and shed little light on motivations. "These terms fail an important test for clinical useful language." They are too imprecise. "We must inquire about specific circumstances under which patients miss pills, distinguish between unintentional and intentional lapses, and ask patients in a non-judgmental way about the motivations for their behavior." "We will rarely learn about medication-taking unless we ask. We must be prepared to respond to their reasonable questions about how much medication-taking is necessary to attain therapeutic goals."

"We must assess what our patients are doing and understand why they do it if we wish to help them change. In this effort, our language is as powerful a tool as the medications we prescribe."

Annals Int Med June 8, 2000; 132: 926-30 "Lingua Medica", Medical Writings, by John F Steiner and Mark A Earnest, University of Colorado Health Sciences Center, Denver. <http://www.annals.org>

Comment:

In a continuing doctor-patient relationship, patients should be encouraged to discuss the changes they make in medication-taking to improve the ongoing process of negotiation and concurrence. I believe these are excellent substitutes for compliance and adherence.

When in practice, I made a valiant attempt to have patients bring all their medications in a brown bag with them at each consultation. I felt that pill counting and review would improve outcomes. The effort failed. Few "remembered" to bring their drugs with them. This article helps to explain why.

This is another step away from the old authoritarian-paternalistic mode of practice to one that recognizes patient autonomy and emphasizes negotiation. A change from being a judge and jury to being a counselor and friend.

The editorialists comment on an interesting past observation regarding patients in the placebo arm of randomized trials. Compared with those who do not take the placebo regularly, those who regularly take the placebo have better outcomes. A difference in the psychological make up of patients in the latter group somehow leads to benefit. I have not read any explanation. RTJ

6-18 UPDATE ON ANTIPLATELET THERAPY FOR STROKE PREVENTION

Many risk factors for stroke have been identified.¹ Many of these can be modified. Individuals who have experienced a TIA or ischemic stroke may reduce risk of subsequent stroke with appropriate management.

Antiplatelet agents are indicated for most individuals after a first stroke or TIA to reduce risk of recurrence.

The FDA and the American College of Chest Physicians (ACCP) now support the use of low dose aspirin (50 to 325 mg daily) alone or in combination with extended-release dipyridamole (*Persantine; Generic*) for secondary prevention.

After a TIA or stroke, the risk of stroke is high, particularly within the first month, and remains elevated over time. "As many as 40% of those who survive a first TIA or stroke will have a subsequent stroke within 5 years."

A meta-analysis reported that antiplatelet prophylaxis reduced risk of non-fatal stroke, non-fatal myocardial infarction, or vascular death by 22% in persons with a history of TIA or stroke.

Antiplatelet agents available include:

Aspirin

Ticlopidine (*Ticlid*)

Clopidogrel (*Plavix*) Preferred over ticlopidine because fewer adverse effects.

Dipyridamole (*Persantine; Generic*)

The European Stroke Prevention Study evaluated antiplatelet drugs in secondary prevention in over 6500 patients. Aspirin alone reduced risk of second stroke by 18%; extended release dipyridamole alone by 16%; the combination by 37%

Low dose aspirin and dipyridamole were well tolerated.

The ACCP recommends the combination of low dose aspirin and extended release dipyridamole (*Aggrenox*) as a potential first-line therapy for secondary prevention.

Archives Int Med June 12, 2000; 160: 1579-82 Review article by Ralph L Sacco and Mitchell S Elkind, College of Physicians and Surgeons of Columbia University, New York <http://archinternmed.com>

1. See table 1 p 1580. The most important are hypertension, atrial fibrillation, lipid abnormalities, diabetes, and carotid stenosis. Heavy alcohol use and smoking also may be modifiable.

My pharmacy quotes a price of about \$80 for 60 tablets of *Aggrenox* (one month supply of combined aspirin and sustained-release dipyridamole.)

Generic for dipyridamole combined with over-the-counter aspirin would cost about \$20 a month.

6-19 PHYSICAL ACTIVITY AND RISK OF STROKE IN WOMEN

Studies of the effect of physical activity on risk of stroke have been conflicting. A dose-response relationship has not been well characterized.

Current guidelines recommend that Americans should accumulate at least 30 minutes of moderate-intensity exercise on most, and preferably all, days of the week.

However, the role of low- and moderate-intensity activities such as walking (compared with vigorous exercise) remains controversial. “If walking is confirmed to provide the same benefits as more vigorous forms of physical activity, it will have important public health implications because walking is the most popular form of physical activity, especially among middle-aged and older women.”

This study assessed the association between physical activity and risk of total stroke and stroke subtypes in women.

Conclusion: Moderate-intensity exercise such as walking was associated with a substantial reduction of total and ischemic stroke in a dose-response manner.

STUDY

1. The Nurses Health study, a prospective cohort study, entered over 72 000 women age 40 to 65 in 1986
2. All were free of cardiovascular disease and cancer.
3. Completed detailed physical activity questionnaires 2 and 6 years later.
4. Outcomes – incident stroke between 1986 and 1994 among quintiles of physical activity level as measured by metabolic equivalent tasks (METs) in hours per week. [*One MET is the amount of energy expended by an individual at rest..*]

RESULTS

1. During 8 years documented 407 incident cases of stroke – 258 ischemic; 67 subarachnoid hemorrhage; 42 intracerebral hemorrhage; 40 unknown type.
2. After controlling for multiple co-variates, increasing physical activity was strongly and inversely correlated with risk of stroke:

A. Total stroke: relative risk lowest to highest MET-hours per week quintiles: 1.00; 0.98; 0.82; 0.74; and 0.66.

B. Ischemic stroke: relative risk lowest to highest: 1.00; 0.87; 0.83; 0.76; 0.52

3. Relative risk of ischemic stroke by walking activity (quintiles):

MET hours per wk	<0.5	0.6-2.0	2.1-3.8	3.9-10	>10
	1.0	0.77	0.75	0.69	0.60

(Walking requires an energy expenditure of 2.0 to 4.5 METs depending on pace.

By my calculations, walking at a moderate pace of 3 miles per hour for 30 minutes daily would add up to about 3 MET hours per week RTJ .)

4. Brisk or strident walking was associated with lower risk compared with average or casual pace.
5. Physical activity was not correlated with subarachnoid hemorrhage or intracerebral hemorrhage.

DISCUSSION

1. In this large prospective cohort study of women, greater leisure-time physical activity was associated with reduced risk of stroke in a dose-response manner.
2. Walking was associated with a substantial reduction in stroke risk. Brisk and very-brisk usual walking pace was independently associated with decreased risk compared with normal or easy pace.
3. “Our study provides strong evidence for a graded inverse relationship between physical activity levels and risk of stroke.”
4. The risk reduction associated with walking was similar to that for coronary heart disease. And for lowering risk for type 2 diabetes.
5. Sedentary women who became active in middle or later life also had a lower risk than their counterparts who remained sedentary.

CONCLUSION

Increasing physical activity levels were associated with substantial reductions in risk for total stroke and ischemic stroke in women. “We observed comparable magnitudes of risk reduction with similar energy expenditure from walking and vigorous activity.”

JAMA June 14, 2000; 283: 2961-67 Original investigation, first author Frank B Hu, Harvard School of Public Health, Boston, Mass. <http://www.jama.com>

6-20 THE ALCOHOL HANGOVER

This article proposed to review the cause, pathophysiologic characteristics, and treatment.

A MEDLINE search found only 108 articles about hangover – in contrast to the several thousand articles about alcohol intoxication. A meta-analysis could not be performed because the few clinical trials were not similar in design or hypotheses.

The alcohol hangover has been termed veisalgia (Norwegian kveis “uneasiness following debauchery” + Greek algia “pain”). (A new terminology for me RTJ)

There is no consensus definition. Most studies have identified a set of common symptoms: headache, anorexia and nausea, diarrhea, tremulousness, poor sense of overall well-being, and fatigue. (Should not vomiting be included? RTJ) Objective criteria have focused on decreased occupational, cognitive, and visual-spatial skill performance. Or on alterations in hemodynamic and hormonal measurements.

Although tachycardia, tremor, orthostasis, cognitive impairment and visual-spatial impairment are frequently observed, they do not capture the overall experience for the patients. The experience remains subjective, varying from person to person and from episode to episode.

To permit a uniform discussion, the authors defined hangover as the presence of at least two of the common symptoms listed above when these symptoms occur after the consumption and full metabolism of alcohol in sufficient quantity to disrupt the performance of daily tasks and responsibilities.

Hangover has substantial economic consequences—decreased productivity, absenteeism, poor job performance. “The *primary morbidity* that affects the light-to-moderate drinkers is the hangover, not the long-term consequences of alcohol abuse.” “Chronic alcoholism is responsible for only a small proportion of the total societal cost of alcohol use.” This is because of the alarming prevalence of veisalgia --- 25% of college students reported a hangover in the previous week; 29% reported losing school time. “More than 75% of persons who have consumed alcohol report that they have experienced hangover at least once.” Fifteen percent experienced hangover at least monthly. “Paradoxically hangover is much more common *in light-to-moderate drinkers* than in heavier drinkers.” Approximately 5 to 6 drinks in an 80-kg man and 3 to 5 drinks in a 60-kg woman will almost always lead to hangover.

Hangover increases risk for injury. Visual-spatial skills are diminished even after alcohol can no longer be detected in the blood. ¹

Nevertheless, hangover has never been shown to effectively deter alcohol consumption. In contrast, hangover may prompt further intake (eg, the “eye opener”).

The hormonal and hemodynamic changes of hangover are distinct from those of alcohol withdrawal. Acetaldehyde, the dehydrogenated product of alcohol metabolism might be responsible for some symptoms. Congeners in the particular alcoholic drink might also cause symptoms. These congeners occur primarily in brandy, wine, tequila, whiskey, and other dark liquors. Clear liquors such as rum, vodka, and gin tend to cause hangover less frequently. In one study a standard dose of alcoholic drink (bourbon vs vodka) 33% of the bourbon drinkers developed severe hangover vs 3% of the vodka drinkers.

Alcohol inhibits the effect of the water-retaining hormone (antidiuretic hormone) on the kidney. This leads to diuresis out of proportion to the volume of fluid ingested. As the blood alcohol concentration decreases and dehydration persists, the serum level of the water-retaining hormone increases in the dehydrated patient. “In our clinical experience hydration attenuates but does not completely relieve hangover symptoms.”

Both hangover and acute intoxication cause metabolic acidosis and various hemodynamic and CNS changes. Hangover manifests as “diffuse cortical depression”; alcohol withdrawal as “general hyperactivity”.

Treatment:

Only a few trials have been conducted. No benefit on hangover severity from propranolol or glucose solution. Tolfenamic acid, a prostaglandin inhibitor and vitamin B6 have been reported to produce some lessening of symptoms.

Clinical implications:

Hangover is common, underdiagnosed, and can have serious physical, psychiatric, and occupational consequences. It is a potentially modifiable cause of morbidity and offers an opportunity for substantial symptom relief.

Screening for hangover severity and frequency may be used to augment strategies for early detection of alcohol dependency. Sons of alcoholic parents are at risk of more frequent hangover. Hangover severity has been used as one of the predictive criteria for alcoholism. Depression and other psychological disorders are more common in patients with hangover.

The most extreme form of hangover is a psychiatric dissociation characterized by irrational behavior. This is known as the “Elpenor” syndrome. Elpenor was a companion of Odysseus. He awoke from a drunken sleep, sprang up, and jumped off a roof, falling to his death. He returned from the dead and begged Odysseus to bury his body. “A sentiment we have often heard echoed by patients with hangover.”

“Hangover is far more than a mere nuisance.” It is common and has substantial morbidity, and societal cost.

Annals Int Med June 6, 2000; 132: 897-902 Original investigation, first author Jeffrey G Weise, University of California, San Francisco <http://www.annals.org/>

Comment:

1 I remember abstracting a study about the effects of one drink in Navy pilots who require an extremely high degree of visual-spatial skills. Many hours after even one drink decreased skills could be identified.

I enjoyed this article. I believe it is the first I have encountered about hangover. It is important. In view of the serious consequences and its predictive value when screening for alcohol dependence, more studies would be welcome. RTJ

RECOMMENDED READING

6-21 PHYSICIAN AND PATIENT SPIRITUALITY: PROFESSIONAL BOUNDARIES, COMPETENCY, AND ETHICS

Spirituality pertains to the ultimate meaning and purpose of life. It has clinical relevance. Clinical studies are beginning to clarify how spirituality and religion can contribute to the coping strategies of many patients with with severe, chronic, and terminal conditions.

Should the physician discuss spiritual issues with his or her patients?

What are the boundaries between the physician and patient regarding these issues?

What are the professional boundaries between the physician and the chaplain?

The physician's duty of beneficence requires respect for the patients spirituality. Deciding how best to respond to a patient's spirituality can raise professional ethical issues.

Annals Int Med April 4, 2000; 132: 578-82 "Perspective" commentary , first author Stephen G Post, Case Western Reserve University, Cleveland Ohio
<http://www.annals.org/>

See also:

""Should Physicians Prescribe Religious Activities?" NEJM June 22, 2000: 1913-16 "Sounding Board", commentary, first author Richard P Sloan, Columbia University College of Physicians and Surgeons, New York
<http://www.nejm.com>

Comment:

During my clinical years, I would always excuse myself immediately when a chaplain or minister entered the patient's room. Now, I would ask at least some patients and clergy, if I expected them to join in prayer, if it would be acceptable for me to linger for a few moments and listen silently. RTJ

REFERENCE ARTICLE

6-22 HEALTH ADVICE AND IMMUNIZATIONS FOR TRAVELERS.

This reference comments on personal precautions and travel-related illnesses, and immunizations.

It presents helpful tables:

- Personal Precautions for Travelers to the Developing World
- Prophylaxis and Self-Treatment for Travel-Related Illness
- Immunizations to Prevent Travel-Related Illnesses
- Web Sites with Health Advice for Travelers.

NEJM June 8, 2000; 342: 1716-25 Review article, first author Edward T Ryan Massachusetts General Hospital and Harvard Medical School, Boston

<http://www.nejm.com>

6-23 EFFECT OF EXERCISE TRAINING ON LEFT VENTRICULAR FUNCTION AND PERIPHERAL RESISTANCE IN PATIENTS WITH CHRONIC HEART FAILURE

Until recently, exercise intolerance among patients with chronic heart failure (**HF**) was regarded as a warning symptom precluding any strenuous exercise. During the past decade it has become appreciated that this approach accelerates physical conditioning and may worsen HF symptom. Carefully designed endurance training programs can improve functional work capacity. Training benefits have been attributed to peripheral adaptations, including enhanced oxidative capacity of muscle and correction of endothelial dysfunction in the muscle vasculature.

Concerns have been raised that training may worsen left ventricular dimensions and contractile function.

This study investigated the incidence of a long-term ambulatory exercise program in patients with stable chronic HF on total peripheral resistance, LV diameter, and stroke volume.

Conclusion: Exercise training was associated with reduction in peripheral resistance and a small improvement in stroke volume and a reduction in cardiomegaly.

STUDY

1. Prospective randomized trial entered 72 men 70 years of age or younger. (Mean = 55).

All had chronic HF documented by symptoms, angiographic evidence of reduced LV function ejection fraction < 40%). All had been clinically stable for at least 3 months. All were taking multiple drugs for HF. Few were taking beta-blockers. None taking spironolactone.

2. Randomized to: 1) 2 weeks of in-hospital ergometer exercise for 10 minutes 4 to 6 times daily,

or 2) no intervention.

3. After discharge home a 6-month ergometer exercise was continued in group 1) 20 minutes daily at 70% of peak oxygen uptake.

RESULTS

1. After 6 months, compared with no intervention, the intervention group had statistically significant improvements in functional class, maximal ventilation, exercise time, and exercise capacity. Also a decreased heart rate and increased LV ejection fraction at rest.
2. Mean total peripheral resistance declined in the intervention group – increased control group.
3. There was also a small but significant reduction in end diastolic LV diameter and a decrease in total peripheral resistance.
4. Three patients (of 36) in the intervention group died suddenly unrelated to exercise. Two patients were admitted to the hospital because of worsening symptoms. They continued training after discharge.
5. Two patients in the control group died.

DISCUSSION

1. Six months of exercise training in patients with moderate-to-severe chronic stable HF:
 - Led to increased stroke volume and a small decrease in left ventricular end diastolic volume.
 - Led to a considerable decrease in peripheral resistance at rest and during exercise.
 - Ie, vasodilatory capacity of small resistance vessels increased, increasing peripheral perfusion.
 - A significant reduction in pulse rate occurred at rest and during exercise.
2. This suggests a considerable reduction in afterload.
3. Note that the study was limited to relatively young men. (Mean age 55.)
4. The effects of training in patients taking beta-blockers could not be assessed.

CONCLUSION

In patients with chronic stable HF, exercise training was associated with a reduction in peripheral resistance and a small, but significant improvement in stroke volume and a reduction in cardiomegaly.

JAMA June 21, 2000; 283: 3095-3101 Original investigation, first author Ranier Hambrecht, University of Leipzig Germany <http://www.jama.com>

Comment:

The authors did not comment on any improvement in health-related quality of life. I believe this would be the most important outcome. RTJ

