

**PRACTICAL POINTERS  
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**ABSTRACTED MONTHLY FROM THE JOURNALS**

**JULY 2000**

**TERMINAL CARE AND THE DOCTRINE OF DOUBLE EFFECT**

**BENEFIT OF TREATING ISOLATED SYSTOLIC HYPERTENSION TO PREVENT STROKE**

**PRIMARY PREVENTION OF CORONARY DISEASE BY DIET AND LIFESTYLE**

**SHOULD WE SCREEN FOR LIPID ABNORMALITIES AT AN EARLY AGE?**

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**THE PATIENT MAY NOT AGREE WITH WHAT YOU THINK IS FUTILE TREATMENT**

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**BRAIN NATRIURETIC PEPTIDE TO TREAT HEART FAILURE**

**SHOULD DDT BE USED FOR HOUSE-SPRAYING TO PREVENT MALARIA?**

**RECOMMENDED READING**

**REFERENCE ARTICLES**

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## **HIGHLIGHTS JULY 2000**

### **7-1 OPIOID USE IN THE LAST WEEK OF LIFE AND IMPLICATIONS FOR END-OF-LIFE DECISION-MAKING**

The Doctrine of Double-effect states that a harmful effect of treatment, even resulting in death, is permissible if it is not intended, and occurs as a side-effect of a beneficial action.

“Our findings indicate that appropriate dose of opioids for symptom control does not shorten life and there is little need to evoke DDE.”

Studies of safety of opioids in cancer patients suggest that problems with respiratory depression are unlikely. Patients most at risk are those who receive increase over 2.5 times their usual dose . Increases above 2.5-fold occurred in only 5 patients in this series.

The DDE may be a useful principle that can offer reassurance when facing difficult treatment decisions. It must be distinguished from euthanasia and its role should not be exaggerated.

The doctrine of double effect need not be invoked to provide symptom control at the end of life.

### **7-2 EFFECT OF TREATING ISOLATED SYSTOLIC HYPERTENSION ON THE RISK OF DEVELOPING VARIOUS TYPES AND SUBTYPES OF STROKE: The Systolic Hypertension In The Elderly Program (SHEP)**

Treatment induced a significant reduction in the incidence of all strokes in patients with isolated systolic hypertension.

Antihypertensive drug treatment which reached the goals of the study (<160 mm Hg) reduced the incidence of both hemorrhagic and ischemic (including lacunar) stroke.

### **7-3 PRIMARY PREVENTION OF CORONARY HEART DISEASE IN WOMEN THROUGH DIET AND LIFESTYLE**

Among women, adherence to lifestyle guidelines involving diet, exercise, and abstinence from smoking was associated with a very low risk of coronary heart disease.

### **7-4 RELATIONSHIPS OF BASELINE SERUM CHOLESTEROL LEVELS IN 3 LARGE COHORTS OF YOUNGER MEN TO LONG-TERM CORONARY, CARDIOVASCULAR AND ALL-CAUSE MORTALITY AND LONGEVITY.**

There was a continuous, graded, long-term relationship between baseline cholesterol levels at ages 18-39 and long-term risk of CHD and CVD

There was substantial absolute risk and absolute excess risk of CHD and CVD death for these younger men. And a longer estimated life expectancy for younger men with favorable levels.

### **7-5 EARLY DETECTION OF HIGH CHOLESTEROL LEVELS IN YOUNG ADULTS**

It is clear "... that early detection of high serum cholesterol levels is a necessary first step in the effort to reduce risk of CHD in the one third of young adults who have total cholesterol levels higher than 200 mg/dL" "The current evidence supports recommendations for measurement of cholesterol levels in adults aged 20 years or older once every 5 years."

### **7-6 DEPRESSION AS A RISK FACTOR FOR NONCOMPLIANCE WITH MEDICAL TREATMENT**

Depressed patients were 3 times more likely to be non-compliant with medical recommendations.

### **7-7 DISCREPANCIES IN THE USE OF MEDICATIONS**

Discrepancies in use of medications were common and involved all classes of drugs. Older age and polypharmacy were the most significant correlates of discrepancy.

### **7-8 CULTURAL AND ECONOMIC FACTORS THAT (MIS)SHAPE ANTIBIOTIC USE:**

#### **The Nonpharmacologic Basis Of Therapeutics**

“Because patient pressure for antibiotic use is a product of contemporary culture, improvement will require a sea change in cultural values.” Patients must be aware of the harms that excessive use of antibiotics brings.

### **7-9 THE PATIENT'S RESPONSE TO FUTILITY**

“Most treatments can be considered futile only within the context of an individual patient's goals for care. If a patient desires aggressive care, the patient is unlikely to consider many treatments futile, even treatments the physician believes are extremely unlikely to be beneficial.”

### **7-10 THE RISE AND FALL OF THE FUTILITY MOVEMENT**

“The judgement that further treatment would be futile is not a conclusion — a signal that care should cease. Instead it should initiate the difficult task of discussing the situation with the patient. The most recent attempts to establish a policy in this area have emphasized processes for discussion of futility rather than the means of implementing decisions about futility. Talking to patients and families should remain the focus of our efforts.”

### **7-11 PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY VERSUS MEDICAL TREATMENT FOR NON-ACUTE CORONARY HEART DISEASE: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS**

The choice of continued medical treatment versus PTCA remains relevant for patients with limited coronary disease and good myocardial function.

PTCA was more favorable regarding subsequent angina (risk ratio 0.70 compared with medical treatment)

But PTCA was less favorable for fatal and non-fatal MI during follow-up (risk ratio = 1.42); for death (RR = 1.32); for subsequent CABG (RR = 1.59); and risk of repeat PTCA (RR = 1.29).

“The procedure should be used only in patients with non-acute CHD in whom angina cannot be controlled by medical treatment. CABG is an alternative in these patients.”

“Clinicians should be restrained in their recommendations for PTCA, reserving the procedure for patients whose symptoms of angina are not well controlled on medical treatment.”

### **7-12 TREATMENT OF STABLE ANGINA**

In patients with severe angina, PTCA is more effective than medical treatment. However, in patients with mild angina, PTCA may not be appropriate. “We will not harm patients by using drug treatment first and using PTCA only if symptoms persist.”

### **7-13 DO PATIENTS WITH SUSPECTED HEART FAILURE AND PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION SUFFER FROM 'DIASTOLIC HEART FAILURE' OR FROM MISDIAGNOSIS? A**

#### **Prospective Descriptive Study**

For most patients referred with a diagnosis of heart failure but with preserved left ventricular systolic function, there is an alternative explanation for their symptoms. A diagnosis of diastolic heart failure was rarely needed. These alternative diagnoses should be rigorously sought and managed.

### **7-14 CAN HEART FAILURE BE DIAGNOSED IN PRIMARY CARE?**

BNP determinations may make it easier to diagnose HF. When added to standard investigations by ECG and chest X-ray BNP may be helpful. I.e, may indicate HF when the ECG and X-ray are equivocal. The most likely initial application will be in triaging symptomatic adults to echocardiography on the basis of a positive test.

If the BNP is negative, HF is unlikely. If the BNP is positive, it may not be certain that HF is present. BNP is more effective in ruling out HF than ruling HF in. A negative test is likely to exclude HF.

### **7-15 ROLE OF EXERCISE TESTING AND SAFETY MONITORING FOR OLDER PERSONS STARTING AN EXERCISE PROGRAM.**

Current guidelines regarding exercise stress testing are not applicable for the vast majority of older persons who are interested in restoring or enhancing their physical function through a program of physical activity and exercise. The goal should be not to deter older persons from participating, but to take prudent precautions. “Relatively few persons aged 75 and older are capable of participating in vigorous or high intensity aerobic training.”

### **7-16 RANDOMISED TRIAL OF EFFECTS OF CALCIUM ANTAGONISTS COMPARED WITH DIURETICS AND BETA-BLOCKERS ON CARDIOVASCULAR MORBIDITY AND MORTALITY IN HYPERTENSION: The Nordic Diltiazem (NORDIL) Study**

Two regimens, one based on the calcium antagonist diltiazem and the other on diuretics, beta-blockers, or both, were equally effective in preventing a combined endpoint of stroke, myocardial infarction, and cardiovascular death over 5 years.

### **7-17 MORBIDITY AND MORTALITY IN PATIENTS RANDOMISED TO DOUBLE-BLIND TREATMENT WITH A LONG-ACTING CALCIUM-CHANNEL BLOCKER OR DIURETIC IN THE INTERNATIONAL NIFEDIPINE GITS STUDY: Intervention As A Goal In Hypertension Treatment (INSIGHT)**

The calcium antagonist nifedipine and co-amiloride (combined diuretic-potassium-sparing drug) were equally effective in preventing overall cardiovascular or cerebrovascular events.

The choice of drug can be decided by cost, tolerability and BP response rather than long-term safety.

### **7-18 DIFFERENCES BETWEEN BLOOD-PRESSURE-LOWERING DRUGS**

The preceding 2 trials demonstrated *no difference* in outcomes between diuretic/beta-blocker based regimens and calcium channel blocker based regimens. Any differences were of marginal significance.

### **7-19 ENVIRONMENTAL AND HERITABLE FACTORS IN THE CAUSATION OF CANCER**

“We conclude that the overwhelming contributor to the causation of cancer in the population of twins that we studied was the environment.” Environment has the principal role in causing sporadic cancer.

Geographic differences, trends over time in the risk of cancer, and detailed studies of migrant populations overwhelmingly implicate environmental exposures as major causal factors, and often identify the responsible carcinogens (eg, tobacco, alcohol, radiation, occupational toxins, infections, diet, drugs). This has led to the widely accepted estimate that 80 to 90 percent of human cancer is due to environmental factors.

**7-20 INTRAVENOUS NESIRITIDE: A Natriuretic Peptide In The Treatment Of Decompensated Congestive Heart Failure.**

In patients hospitalized for treatment of decompensated CHF, the brain natriuretic peptide, nesiritide improved hemodynamic function and clinical status. "Intravenous nesiritide is useful for the short-term treatment of decompensated congestive heart failure."

**7-21 DDT HOUSE SPRAYING AND RE-EMERGING MALARIA**

"We recommend that the global response to burgeoning malaria rates should allow for DDT residual house spraying where it is known to be effective and necessary."

**RECOMMENDED READING**

**7-8 CULTURAL AND ECONOMIC FACTORS THAT (MIS)SHAPE ANTIBIOTIC USE:**

**7-10 THE RISE AND FALL OF THE FUTILITY MOVEMENT**

**7-19 ENVIRONMENTAL AND HERITABLE FACTORS IN THE CAUSATION OF CANCER**

**7-24 PROFESSIONALISM: An Ideal To Be Sustained**

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**7-22 HYPERTENSIVE EMERGENCIES**

**7-23 DRUG THERAPY FOR BREAST-FEEDING WOMEN**

**7-25 NINE PRINCIPLES OF FAMILY MEDICINE**

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**7-1 OPIOID USE IN THE LAST WEEK OF LIFE AND IMPLICATIONS FOR END-OF-LIFE DECISION-MAKING**

Concern continues about use of opioids at the end of life, and in particular their possible role in shortening life. Some fear that the doctrine of double-effect (**DDE**) may be used as a cover for euthanasia.

*[DDE states that a harmful effect of treatment, even resulting in death, is permissible if it is not intended, and occurs as a side-effect of a beneficial action.]*

This study assessed whether symptom control with opioids is associated with shortening of life, and how often the DDE is relevant in palliative care.

Conclusion: DDE need not be invoked to provide symptom control at the end of life.

## STUDY

1. Retrospective case-note review of 238 consecutive patients (mean age 69) who died in a hospice unit. Median patient stay was 9 days.
2. Recorded opioid dose (expressed as parenteral morphine equivalents) during the last week of life. Any change in dose was calculated for each 24 hour period. Analyzed distribution of any 2-fold or more increase in dose. Compared characteristics of patients who received a marked increase in dose with those who received a lesser dose.
3. Defined a marked increase in dose as: 1) a greater than 1.5-fold increase in dose over the last 48 hours of life, or 2) a greater than 30 mg increase in dose per 24 hours, or 3) a greater than 3-fold increase in the last week.

## RESULTS

1. 89% of patients received opioids in the last 24 hours compared with 61% at admission.
2. Mean daily dose increased from 42 mg to 56 mg over the last 7 days.
3. The proportion of patients receiving a greater than 2-fold increase per 24 hours was small, ranging from 3% to 7%. Increases were evenly distributed over the week.
4. Patients who received a marked increase in dose (compared with those who received no increase) showed no survival difference in time from admission, frequency of unexpected death, or description of death. They were more likely to receive opioids for pain and more likely to receive sedatives.
5. In no case could DDE be implicated. The reason for the increase was recorded in all cases and the deterioration in condition was noted before the change in dose.

## DISCUSSION

1. "Our findings indicate that appropriate dose of opioids for symptom control does not shorten life and there is little need to evoke DDE."
2. Studies of safety of opioids in cancer patients suggest that problems with respiratory depression are unlikely. Patients most at risk are those who receive increase over 2.5 times their usual dose. Increases above 2.5-fold occurred in only 5 patients in this series.
3. The DDE may be a useful principle that can offer reassurance when facing difficult treatment decisions. It must be distinguished from euthanasia and its role should not be exaggerated.

## CONCLUSION

The doctrine of double effect need not be invoked to provide symptom control at the end of life.

Lancet July 29, 2000; 356: 398-99 Original investigation by Andrew Thorns and Nigel Sykes, St Christopher's Hospice, London. [www.thelancet.com](http://www.thelancet.com)

Comment:

I have struggled with the concept of the doctrine of double effect.. I now have it clarified in my mind.

The clinician's intent must always be, and only be, on providing comfort to the patient and family.

Euthanasia rests on "intent" to kill, not pain relief.

Patients who are in pain at the end of life should receive enough (and not more) of the dose of morphine to effectively relieve pain. The study suggests strongly that higher doses of opioids are rarely used. Should they die during the course of this approach to comfort care, we must not believe that we have performed euthanasia. The DDE should be invoked only when the dose of morphine needed to relieve pain and death caused by that dose are in equipoise. This occurs rarely.

Euthanasia occurs when the patient dies when we *continue* to administer opioids above and beyond the dose needed for comfort, and continue to give more and more until the patient dies. Intent to cause death is then evident. RTJ

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## **7-2 EFFECT OF TREATING ISOLATED SYSTOLIC HYPERTENSION ON THE RISK OF DEVELOPING VARIOUS TYPES AND SUBTYPES OF STROKE: The Systolic Hypertension In The Elderly Program (SHEP)**

The first completed trial of isolated systolic hypertension (**ISH**) was published in 1991.<sup>1</sup> Treatment of ISH reduced strokes by 36%, myocardial infarctions by 27%, cardiovascular disease by 32%, and total mortality by 13%.

This study investigated effects of drug treatment of ISH on incidence of stroke by type and subtype, timing of strokes, case-fatality rates, stroke residual effects, and relationships of attained systolic BP (**SBP**) to stroke incidence.

Conclusion: Drug treatment of ISH reduced incidence of both hemorrhagic and ischemic (including lacunar) stroke.

### **STUDY**

1. Multicenter, randomized, double-blind, placebo-controlled trial entered over 4500 multi-ethnic men and women over age 60. Those with atrial fibrillation were excluded.
2. All had ISH (systolic > 160 and diastolic < 90). Baseline BP averaged 170/77; 57% had systolic

BP between 160-169; 27% between 170-179; and 15% were 180 or higher.

3. Ten percent had diabetes, 5% had a history of myocardial infarction, and 1.4% had experienced stroke.
4. Randomized to:
  - 1) Active drug therapy:
    - A. Chlorthalidone (a diuretic) 12.5 mg/d. Dose could be doubled if systolic BP not controlled.
    - B. Atenolol (beta-blocker) 25 mg/d added if BP not controlled by chlorthalidone.  
Dose could be doubled.
  - 2) Placebo. (However, in this group use of antihypertensive drugs gradually rose to 44% at year 5.)
5. Goal of treatment = decrease in baseline SBP of > 20 mm Hg or to a systolic BP < 160.
6. Follow-up = 5 years

## RESULTS

1. At the end of the trial, about 25% of the active treatment group were receiving 2 drugs.
2. BP declined from baseline by a mean of 26/9 mm Hg in the active treatment group and by 15/4 in the placebo group.
3. At the end of the trial, 65% of the treatment group achieved the goal vs 40% of the placebo group.
4. Stroke outcomes:
  - A. Ischemic stroke -- 85 participants in the active treatment group had ischemic stroke vs 132 in the placebo group (adjusted relative risk = 0.63).  
Subtypes of ischemic stroke: 1) lacunar stroke – 23 vs 43 (RR = 0.53); embolic – 9 vs 16 (RR = 0.56); atherosclerotic 13 vs 13; unknown type – 40 vs 60 (RR = 0.64)
  - B. Hemorrhagic stroke -- 9 vs 19 (RR = 0.46)
5. Treatment benefit was observed within 1 to 2 years.
6. Stroke incidence significantly decreased in participants attaining study-specific systolic BP goals.

## DISCUSSION

1. Hypertension is characterized by microaneurysms, lipohyalinosis, and fibrinoid necrosis, particularly in penetrating arteries that supply basal ganglia, cerebral deep white matter, and pons. These are the sites of lacunar stroke and intraparenchymal hemorrhage, the 2 subtypes of stroke most strongly associated with hypertension. Both are decreased by treatment of systolic hypertension..
2. The lack of treatment effect on incidence of atherosclerotic stroke was unexpected.
3. Decreasing the SBP to less than 160 mm Hg lowered the stroke rate by one third. Decreasing

SBP to less than 150 lowered the rate even more. Decreasing the SBP to less than 140 did not have a significant effect, perhaps because few participants achieved that goal.

4. Some in the placebo group reached the goal for SBP. In these individuals, reduction in stroke was similar to those in the active treatment group. “This strongly suggests that the level of attained SBP rather than treatment or a particular antihypertensive drug was the paramount factor in reducing stroke incidence.”

## CONCLUSION

Treatment induced a significant reduction in the incidence of all strokes in patients with isolated systolic hypertension.

Antihypertensive drug treatment which reached the goals of the study (<160 mm Hg) reduced the incidence of both hemorrhagic and ischemic (including lacunar) stroke.

JAMA July 26, 2000; 284: 465-71 Original investigation by the Systolic Hypertension in the Elderly Program (SHEP) Cooperative Research Group, first author H Mitchell Perry Jr. [www.jama.com](http://www.jama.com)

1 JAMA 1991; 265: 3255-64

Lacunar stroke was defined as either: 1) a small (< 2 cm in diameter) lesion, correlating with symptoms or signs of stroke, seen on imaging in deep structures of the hemisphere or in the pons; or 2) if brain imaging showed no lesion responsible for the signs and symptoms and the patient had pure motor hemiparesis, pure sensory stroke, dysarthria, clumsy-hand syndrome, or ataxia hemiparesis syndrome.

### Comment:

Many in the placebo group were treated (antihypertensive drugs not specified) and achieved the treatment goal. If none had been treated, comparative results of treatment would have been even more striking.

Recognition of the adverse effects of isolated systolic hypertension and the benefits of treatment is one of the greatest advances in therapeutics over the past 10 years. RTJ

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## **7-3 PRIMARY PREVENTION OF CORONARY HEART DISEASE IN WOMEN THROUGH DIET AND LIFESTYLE**

This study assessed the effect of a combination of lifestyle practices on the risk of coronary heart disease (**CHD**). It estimated the proportion of coronary events that could potentially be prevented by adherence to a set of dietary and behavioral guidelines.

Conclusion: Adherence to lifestyle practices was associated with a very low risk.

## STUDY

1. The Nurses' Health Study followed over 84 000 women (age 30 to 55 at baseline) for 14 years.
2. At baseline, all were free of diagnosed cardiovascular disease, cancer, and diabetes.
3. Updated information on diet and lifestyle periodically.
4. Defined individuals at low risk as those not currently smoking; with a body mass index below 25; consuming at least a half a drink of alcoholic beverage per day; engaging in moderate-to-vigorous physical activity (including brisk walking) for at least 30 minutes daily on average; and scoring in the highest 40% of the cohort for consumption of cereal fiber, marine n-3 fatty acids, folate (including supplements), and maintaining a high ratio of poly-unsaturated to saturated fats, a low trans fat intake, and a low-glycemic load diet.
5. All of these risk factors are modifiable.

## RESULTS

1. During 14 years follow-up documented 1128 major coronary events (298 deaths, and 832 non-fatal myocardial infarctions).
2. Only 3% of the women were in the low-risk category. Compared with all other women, they had a relative risk of coronary events of 0.17.
3. The 7% with 4 low-risk factors (diet, no smoking, exercise, low BMI) had a RR of 0.34; the 13% with 3 low-risk factors (diet, no smoking, exercise) had a RR of 0.43.
4. 80% of coronary events in the study cohort could be attributed to lack of adherence to the low-risk pattern.

## DISCUSSION

1. By simultaneously examining the effect of several lifestyle variables, the study took into account the clustering of healthful types of behavior.
2. "Middle-aged women, who did not smoke cigarettes, were not overweight, maintained the healthful diet described above, exercised moderately or vigorously for half an hour a day, and consumed alcohol moderately, had an incidence of coronary events that was more than 80 percent lower than that in the rest of the population."

3. The study did not consider consumption of nuts, linolenic acid, vitamin B6, vitamin E, or use of aspirin and postmenopausal hormones. "Larger reductions in risk might be possible with these added preventive factors." Treatment of hypertension or dyslipidemia were not considered.

## CONCLUSION

Among women, adherence to lifestyle guidelines involving diet, exercise, and abstinence from smoking was associated with a very low risk of coronary heart disease.

NEJM July 6, 2000; 343: 16-22 Original investigation, first author Meir J Stampfer, Brigham and Women's Hospital and Harvard Medical School, Boston Mass. [www.nejm.com](http://www.nejm.com)

### Comment:

I believe the *primary* responsibility of primary care clinicians is to promote a healthy lifestyle. Indeed, if the population were to adopt the favorable lifestyle described, this would improve the public health more than any high tech intervention developed in the past 25 years. As a first step clinicians must adopt the lifestyle themselves. It is notable that only 3% of women in this study had a perfect score.

The message is not new. It requires constant repetition.

This is the first large epidemiologic study of this type I have encountered which included small amounts of alcohol as a protective factor. RTJ

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## **7-4 RELATIONSHIPS OF BASELINE SERUM CHOLESTEROL LEVELS IN 3 LARGE COHORTS OF YOUNGER MEN TO LONG-TERM CORONARY, CARDIOVASCULAR AND ALL-CAUSE MORTALITY AND LONGEVITY.**

For middle-aged populations, serum cholesterol is an established major risk factor for coronary heart disease (**CHD**). For younger adults, there has been debate about the value of detecting and treating hypercholesterolemia.

This study provides long-term data from 3 prospective studies (see text for citations) from which cohorts of younger men were selected to assess risks of CHD related to cholesterol levels.

Conclusion: There was a continuous, graded relationship between baseline cholesterol levels (at ages 18-39) and long-term risk of CHD.

## STUDY

1. Three prospective studies entered a total of over 81 000 men age 18-39. None had a history of diabetes or myocardial infarction.
2. Main outcome measures: cause-specific mortality during 16, 25, and 34 years of follow-up in relation

to cholesterol levels at baseline.

## RESULTS

1. Death due to CHD accounted for 26%, 34%, and 28% of all deaths. Death due to cardiovascular disease accounted for 39%. 34%, 42%, of all deaths.
2. There was a strong gradient of relative mortality risk as cholesterol levels rose:

Baseline cholesterol	Relative mortality from CVD
< 160	1.00
160-199	2.12
200-229	3.18
240-279	4.47
≥ 280	8.53

3. Men with unfavorable cholesterol levels (200 to 239 mg/dL; 5.17 to 6.18 mmol/L) had strong gradients of relative mortality risk vs those with favorable levels (< 200 mg/dL).
4. For men with levels 240 or greater, CHD mortality was 2.15 to 3.63 times greater; CVD mortality was 2.1 to 2.87 greater; all-cause mortality 1.31 to 1.49 times greater.
5. Hypercholesterolemic men had an age-adjusted absolute risk of CHD death of 15 per 1000 in 16 years; 59 per 1000 in 25 years; 90 per 1000 in 34 years.
6. Absolute excess risk (compared with those with favorable levels) was 12, 44, and 81 per 1000.
7. Men with favorable baseline levels had an estimated greater life expectancy of 3.8 to 8.7 years.

## DISCUSSION

1. In these cohorts of young men, there were strong, continuous, graded, and independent relationships between baseline cholesterol levels at ages 18-39 and long-term risk of death due to CHD and CVD.
2. Substantially shorter life-expectancy (4 to 9 years) was observed for those with levels ≥ 240. (These estimates are understated because they are based on only one cholesterol measurement per person at baseline, tending to produce miscalculation.)
3. This and other studies support population-wide efforts to identify children, teenagers, and young adults with unfavorable levels (and other risk factors) so that early therapeutic efforts can be instituted.

## CONCLUSION

There was a continuous, graded, long-term relationship between cholesterol levels and risk of CHD and CVD in men who at baseline were ages 18-39.

There was substantial absolute risk and absolute excess risk of CHD and CVD death for these younger men. And a longer estimated life expectancy for younger men with favorable levels.

JAMA July 19, 2000; 284: 311-18 Original investigation, first author Jeremiah Stamler, Northwestern University Medical School, Chicago. [www.jama.com](http://www.jama.com)

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## **7-5 EARLY DETECTION OF HIGH CHOLESTEROL LEVELS IN YOUNG ADULTS**

*(This editorial comments and expands on the preceding study.)*

The previous study again raises the question about screening for high cholesterol levels in young adults. The findings confirm and reinforce previous reports that high levels in young adults carry higher risk of CHD later in life. Is early detection in the clinical setting warranted?

Several arguments can be made in favor of early detection of high cholesterol levels (more specifically high LDL-cholesterol levels). "Without some elevation of LDL cholesterol, CHD is rare, even when other risk factors are present." Prospective studies strongly suggest that even moderate reductions in cholesterol levels by diet will substantially reduce long-term risk for CHD. Moreover, costs of early detection are relatively low. Benefit for a portion of affected individuals should be substantial.

Some arguments against early screening: The number of people who will be identified will be low; efficacy of long-term dietary intervention has not been established convincingly in controlled trials. Long-term drug intervention is costly and may be associated with adverse effects. Perhaps interventions can be started later in life without loss of benefit.

Counterarguments: Prevalence of borderline levels (200-250 mg/dL) is quite high in young US men; dietary modifications over the past 3 decades have lowered cholesterol levels significantly. "The demonstrated safety and declining costs of cholesterol-lowering drugs weakens the argument against their use in select young adults."

To some investigators, unless a question has been answered by a controlled trial, no conclusion can be drawn. Ie, when there is no such clinical trial data, evidence is considered insufficient to recommend for or against intervention. "However, important clinical issues must be addressed, even if they cannot be answered by controlled clinical trials or if data from controlled trials are not available." Then other lines of evidence must be considered. These include primacy of high cholesterol in atherogenesis;

progression of atherosclerosis in young adults; unacceptably high incidence of CHD later in life; and long-term predictability of cholesterol levels.

It may be difficult for primary care physicians to take the time to counsel seemingly healthy adults about dangers to their health that are 20 to 40 years away. (*And to engage young adults to understand, concur with, and accept a long-term treatment plan. This may be largely unsuccessful, but a few may benefit greatly. RTJ* )

Discovery of an abnormal lipid pattern may lead to screening for risk factors which make up the "metabolic syndrome" — low HDL-cholesterol, abnormal glucose metabolism, high-normal BP, overweight. And to other risk factors — smoking, poor dietary habits, and sedentary life-style. "It is no longer appropriate to ask whether cholesterol should be measured independently of other risk factors."

It is clear "... that early detection of high serum cholesterol levels is a necessary first step in the effort to reduce risk of CHD in the one third of young adults who have total cholesterol levels higher than 200 mg/dL" "The current evidence supports recommendations for measurement of cholesterol levels in adults aged 20 years or older once every 5 years."

JAMA July 19, 2000; 284: 365-67 Editorial by Scott M Grundy, University of Texas Southwestern Medical Center, Dallas. [www.jama.com](http://www.jama.com)

Comment:

Screening for lipid disorders and other risk factors is an important responsibility and challenge for primary care clinicians and their younger male patients. Whether to screen younger women is more debatable. Total cholesterol concentrations can be misleading in premenstrual women and postmenopausal women taking hormone replacement. Total may be high due to a high HDL-cholesterol. The HDL/LDL ratio may be normal. Indeed, I believe "total cholesterol" should now be abandoned as a screen in favor of a lipid profile including a HDL/LDL ratio or at least a HDL/non-HDL ratio in both men and women.

Screening younger patients may be made more productive by concentrating on individuals who have other obvious risk markers and a family history of established CHD and abnormal lipid patterns — and especially diabetes. Occasionally a metabolic disorder related to extraordinarily high cholesterol levels may be discovered, to the benefit of all members of the family.

As with any abnormal screen, the patient risks "labeling" and undue concern about positive findings. Reassurance is the other side of the screening coin. Reassurance after a negative screen is welcome. For those with positive screens reassurance is provided mainly by effective treatment and by concerned follow-up. Fortunately, changes in life-style patterns can lead to adequate control of the lipid pattern in

some young patients. Many improvements in foods available to the general public in the past 10 years lead to more favorable lipid patterns — lower saturated fat and trans fat content, added sterols and stanols, olestra. Dietary treatment is easier and more palatable. Fiber and soy protein can be added with benefit.

What should be done about drug treatment?

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## **7-6 DEPRESSION AS A RISK FACTOR FOR NONCOMPLIANCE WITH MEDICAL TREATMENT**

Depression of all degrees occurs in at least 25% of patients undergoing medical treatments. Prevalence is greater in those with significant health problems.

Anxiety and depression commonly co-exist. Both are associated with diminished health status and lower quality-of-life. Depression is also associated with higher rates of health care utilization and limitations in daily functioning.

Both anxiety and depression may complicate treatments of medical conditions. And lead to poorer outcomes.

This study asks: To what extent are depression and anxiety linked to poor adherence with treatment recommendations? Non-adherence manifests as not using medications properly, forgetting or refusing to follow a diet, not engaging in proper exercise, canceling or not attending appointments, and persistence in adverse lifestyles. Non-adherence has a consistently negative effect on treatment outcomes.

Conclusion: Depressed patients were three times more likely to be non-adherent as non-depressed patients.

### **STUDY**

1. Literature search found 12 studies linking depression to the degree of patient adherence with a medical regimen. And 13 studies linking anxiety with compliance. All studies involved medical regimens recommended by a non-psychiatrist physician to a patient not being treated for anxiety, depression or a psychiatric illness.
2. Arrived at a quantitative assessment of adherence.

### **RESULTS**

1. The association between anxiety and non-adherence was variable and small.
2. The association between depression and non-adherence was substantial and significant.

(Odds ratio = 3 compared with non-depressed patients. )

## DISCUSSION

1. Eleven of the 12 studies were consistent in linking non-adherence with depression.
2. Why might depression increase non-adherence?
  - A. Depression involves a degree of hopelessness. Adherence might be difficult or impossible for patients who hold little optimism that any action might be worthwhile.
  - B. Depression is often accompanied by considerable social isolation and withdrawal. This might remove support of family members who are needed to help with adherence.
  - C. Depression might be linked to cognitive dysfunction which impedes remembering and following through with recommendations.
3. In contrast, anxiety had unclear relationship to adherence.
4. “Recognizing that a patient might be depressed could help a physician manage his or her frustration<sup>1</sup> at that patient’s non-compliance and thus improve the physician-patient relationship.”
5. For patients beginning a course of treatment for chronic disease, screening for depression might prove to be a useful identifier of possible future non-adherence and might suggest closer monitoring. Alternatively, non-adherence should raise suspicion of co-existing depression.
6. Recognition of depression as a risk factor for non-adherence carries the potential to improve medical applications, reduce patient disability, enhance patient functioning, and improve health outcomes.

## CONCLUSION

Depressed patients were 3 times more likely to be non-compliant with medical recommendations.

Archives Int Med July 24, 2000; 160: 2101-07 Original investigation, first author M Robin DiMatteo, University of California, Riverside. [www.archinternmed.com](http://www.archinternmed.com)

### Comment

1. Frustration and irritation at the patient are the wrong responses. Understanding and negotiation are the right responses. One of the greatest mistakes I made during my clinical career occurred when I expressed anger at a patient for his lack of adherence to the prescribed regimen. He in turn became angry and withdrew from my care. I made no attempt to understand the reason for his non-adherence or to negotiate a reasonable compromise.

There are many pitfalls between applying the best clinical evidence of efficacy of a treatment regimen and the individual patient's acceptance and adherence to the regimen:

1. Financial constraints
2. Disbelief in effectiveness
3. Development of adverse effects and toxicity
4. Age, depression, forgetfulness, dementia (even if mild) , lack of family support, too complicated a regimen.
5. Ethnic differences, illiteracy, lack of proper instruction and understanding
6. Use of drugs and herbs purchased over-the-counter which increase or decrease effects of the physician-prescribed drug.
7. Withdrawal for personal reasons.

In addition, often patients simply may not fit the evidence from randomized trials. They would have been eliminated from the trial by the exclusion criteria. Then a reasonable extrapolation is often made when prescribing the regimen to an individual, but without assurance of effectiveness for that individual.

Remember that any regimen found effective in a randomized trial will not benefit all patients who closely fit entrance criteria and are completely adherent to the regimen. For example, the number needed to treat to benefit one patient over X years is often over 10. Thus 9 patients will be treated without benefit, while bearing the cost and risking adverse effects. A NNT of 3 is unusually low. Even then, many patients will not benefit.

As powerful as "Clinical Evidence" is, its application to an individual patient does not ensure benefit.

As has been stated, "Science can tell us nothing about an individual patient". The great challenge for primary care clinicians is to use "best judgement" when applying the "best evidence" to the patient in front of them . RTJ

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## **7-7 DISCREPANCIES IN THE USE OF MEDICATIONS**

*Their Extent and Predictors in an Outpatient Practice.*

“Misuse of medications is a major cause of morbidity and mortality.” This is especially prevalent among the elderly who are especially vulnerable, and often have several medical conditions for which multiple medications are prescribed.

This study asks: What is the frequency of, and factors associated with, discrepancies between what doctors prescribe and what patients actually take?

Conclusion: Discrepancies were common and involved all classes of medications.

## STUDY

1. Compared medication bottles and patient's reported use of medications with physician's records in 312 outpatients.
2. Assessed the magnitude of discrepancies between medications the patients actually took and the documented record of prescription.
3. Most patients were responsible for administering their own medications. Most had other physicians who participated in their care.
4. Discrepancies included; taking medications not prescribed, not taking a recorded prescribed medication, and differences in dosage.

## RESULTS

1. Discrepancies were present in 76% of patients – a total of 545 discrepancies in 239 patients.
2. Discrepancies were more likely: 1) In older patients, 2) in those having other physicians participate in their care, and 3) in those for whom more drugs were prescribed. (Polypharmacy)
3. Most discrepancies were attributable to taking medications that were not prescribed.
4. Other discrepancies were attributed to patients not taking a recorded drug, or to differences in dosage.
5. "Over-the-counter medications were the single largest category of discrepancies. "
6. The study recorded comments from patients regarding their concerns:
  - A. They wanted more details from their physician about how the prescribed drug would help their symptoms and how it would interact with other medications.
  - B. Concerns about adverse effects. These were often vague, such as "feeling blah", feeling "not myself", the medication might "be too much". Also loss of libido and liver toxicity.
  - C. Obstacles of convenience and cost. "Convenience in talking and filling prescriptions was more important to our patients than medication costs."
  - D. Influence of multiple physicians: The majority of patients' comments focused on problems of having multiple physicians involved in their care.

## DISCUSSION

1. In the majority of patients in an outpatient private practice there was considerable discrepancy between prescribed medications and those actually taken.
2. Discrepancy should be differentiated from non-adherence.
3. Discrepancies included all medications – prescription and non-prescription. In one third of

patients, discrepancies involved over-the-counter medications or herbal therapies which patients were taking without informing their physician. “Adverse effects from such therapies are not necessarily trivial.”

4. The majority of discrepancies occurred with prescription drugs and a full quarter with cardiac drugs.
5. “The more drugs a patient takes, the more likely there will be a discrepancy.”
6. Miscommunication between physicians and between physician and patient plays a major role.
7. “A long-term patient-physician relationship did not diminish the likelihood of medication discrepancy.”
8. “A compulsive, specific, and systematic review of the patient’s medication bottles should become a standard element of the patient’s care.” <sup>1</sup>
9. “Critical review of the medication should emphasize the simplest, most parsimonious prescribing regimen.”

## CONCLUSION

Discrepancies in use of medications were common and involved all classes of drugs. Older age and polypharmacy were the most significant correlates of discrepancy.

Archives Int Med July 24, 2000; 2129-34 Original investigation, first author Susanna E Bedell, Lown Cardiovascular Center and Harvard Medical School, Boston, Mass. [www.archinternmed.com](http://www.archinternmed.com)

### Comment

**1** This sounds simple, but in my experience, is difficult. Patient often “forget” to bring their medications with them. They may be taking over-the-counter medications and alternative drugs and herbs they do not wish to disclose.

A difference between what is prescribed and what patients actually take is the rule, not the exception, especially for long-term treatment. Primary care physicians must develop a trust and negotiate with patients an understanding of the importance of full disclosure of their medical regimen. This must be done non-judgmentally. RTJ

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## RECOMMENDED READING

**7-8 CULTURAL AND ECONOMIC FACTORS THAT (MIS)SHAPE ANTIBIOTIC USE:  
The Nonpharmacologic Basis Of Therapeutics**

“Drug use historically has reflected the highest principles of science as well as strikingly irrational behavior. This heterogeneity has been particularly vivid in the case of antibiotics.”

Antibiotics tap into some of our most deeply held beliefs about bodily integrity and invasion. Other than certain vaccines, antibiotics are the only drug class whose use influences not just the patients being treated but the entire ecosystem in which he or she lives, with potentially profound consequences.

In their psychosocial dimension, medications can have properties that transcend pharmacology and take center stage in some clinical situations. “Providing a patient with drugs is an interpersonal as well as a biochemical intervention.” Writing a prescription signifies that the physician has made a diagnosis and that treatment is possible. A prescription officially assigns the patient to the sick role, with all its benefits and responsibilities. In a real sense, the drug prescription prolongs the patient-physician encounter by enabling the patient to ingest a “dose of the doctor” several times a day. This perspective helps to explain the “drug hunger” that many symptomatic patients bring to the physician visit, in which they feel satisfied only by receiving a prescription.

It also can act as a termination strategy for an office visit, a sign that the visit has been consummated, the encounter complete, and it is time for the patient to move on. “A prescription for an antibiotic is often seen as the quickest way to end the visit of a patient with symptoms of possible infection. This may be more applicable now that physicians are called upon to maximize the number of patients seen per day.

Concern about patient satisfaction, the drive to shorten the office visit, and aggressive marketing by drug companies, set the stage for the demand and receipt of astoundingly large quantities of unnecessary antibiotics.

Many randomized trials have found that outcomes of acute bronchitis, coughs and upper respiratory illnesses are no better in typical patients taking antibiotics than in those given placebo. However, diagnostic uncertainty does play a role.

“Because patient pressure for antibiotic use is a product of contemporary culture, improvement will require a sea change in cultural values.” Patients must be aware of the harms that excessive use of antibiotics brings. “Fortunately, enough motivations relate to the patient’s own well-being, including the desire to avoid such common side effects as rash and diarrhea, and the recognition that unwanted organisms may infect not only one’s neighbor, but also oneself (for example candidal vaginitis or *Clostridium difficile* colitis).

The editorialists go on to discuss physician and patient resources promoting rational antibiotic prescribing. (*Table 2 p 133 lists several web sites containing practical information.*)

Good patient education material is easy to access from many web sites, and can be downloaded and given to patients as a kind of “unprescription”. In this case the “dose of the doctor” is a dose of knowledge rather than a drug.

Annals Int Med July 18, 2000; 133: 128-134 "Academia and Clinic" editorial by Jerry Avorn and Daniel H Solomon, Brigham and Women's Hospital, Boston Mass. [www.annals.org](http://www.annals.org)

Comment:

I believe that the physician's (especially younger ones) fear of "missing" an important infection which may progress rapidly and cause complications does influence prescribing. In this respect, giving an "if" prescription is an acceptable way to avoid patient dissatisfaction while possibly improving the therapeutic intervention. The physician gives a prescription (including antibiotics when it seems that there is a possible, but questionable, chance that the disease may be an infection which will respond) — at the same time telling him not to have it filled for 2 or 3 days, and reassuring him that the illness is likely to subside, and the antibiotic unnecessary. When this is done, most prescriptions will not be filled. RTJ

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## 7-9 THE PATIENT'S RESPONSE TO FUTILITY

Bioethicists have debated for years about the concept of medical futility. There is no clear legal precedent about withholding futile care against a patient's wishes. "Withholding futile treatments supports the ethical principles of both non-maleficence (do no harm) and beneficence (relieve suffering)."

Futility is difficult to define. One definition: Situations in which proposed treatments will fail to prolong quality life, fail to achieve a critical physiologic effect on the body, or fail to result in a therapeutic benefit for the patient.

Another definition: "If a treatment merely preserves permanent unconsciousness or cannot end dependence on intensive medical care, the treatment should be considered futile."

In practice, however, the concept of futility is applied broadly and often incorrectly. Decisions about which treatments are futile almost always need to be based on the patient's goals for medical care. "Only in the strictest interpretation of futility, treatments that do not offer any physiological benefit, can we apply it broadly without regard to the variability of patients' values."

The editorialist refers to an article in this issue of *Archives* of patients with advanced AIDS. A structured interview assessed patients' responses to hypothetical situations in which they had less than 3 months to live and had developed severe pneumonia. They were told that their physician thought that initiating life support such as mechanical ventilation would be futile (ie, the patient would be unlikely to survive to get off life-support). Would it be acceptable for their physicians to make them comfortable without offering life-support? Results: while the majority felt it would be acceptable, 13% answered it

would definitely not, or probably not, be acceptable. "These patients rejected the medical futility rationale; withholding life support would contradict their goals."

The editorialists believe that "Most treatments can be considered futile only within the context of an individual's goals for care. If a patient desires aggressive care, the patient is unlikely to consider many treatments futile, even treatments the physician believes are extremely unlikely to be beneficial."

Archives Int Med June 12, 2000; 160: 1565-66 Editorial, first author David C McGee, Stanford University Medical Center, Stanford CA. [www.archinternmed.com](http://www.archinternmed.com)

See also:

"The Attitudes of Patients with Advanced AIDS Toward Use of The Medical Futility Rationale in Decisions to Forego Mechanical Ventilation" Archives Int Med June 12, 2000; 160: 1597-1601

"Why Don't Patients and Physicians Talk About End-Of-Life Care?" Archives Int Med June 12, 2000; 160: 1690-96

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## RECOMMENDED READING

### 7-10 THE RISE AND FALL OF THE FUTILITY MOVEMENT

*(This editorial comments further.)*

Futile care in hospitals is still very much an issue, yet doctors today are no more empowered to unilaterally declare a treatment futile than they were 15 years ago. No consensus has been achieved. Who has the right to decide whether a medical care is futile? Some have argued that no one is better able to make judgements about what is beneficial to patients than patients themselves. Physicians may be best suited to frame the choices by describing prognosis and quality of life. Beyond that, they run the risk of giving "opinions disguised as data".

The Acute Physiology and Chronic Health Evaluation (APACHE) system proved to be valuable for prognosis. But, it provides prognostication for groups, not for individuals. The information represents an adjunct to discussions about futility, not a solution to the problem.

In individual cases where disagreement persists, steps can be made to resolve the conflict by continuing conversations and negotiation. Multidisciplinary committees can be used before resorting to the courts. (Indeed, the courts have not upheld the right of physicians to make unilateral judgements about futility.) If conflict remains and physicians feel strongly about the futility of continuing treatment, there is the possibility of transferring the patients' care to another institution.

"The judgement that further treatment would be futile is not a conclusion — a signal that care should cease. Instead it should initiate the difficult task of discussing the situation with the patient. The most

recent attempts to establish a policy in this area have emphasized processes for discussion of futility rather than the means of implementing decisions about futility. Talking to patients and families should remain the focus of our efforts."

NEJM July 27, 2000; 343: 293-96 "Sounding Board". editorial, first author Paul R Helft, University of Chicago IL [www.nejm.com](http://www.nejm.com)

Comment:

Fortunately, in primary care, the dilemma arises rarely. There is no dispute about keeping the terminal patient comfortable. The problem then usually is self-determining.

In cases of competent patients, I believe decisions are much less difficult than in cases of incompetent patients. (Eg, infants and demented elderly.) The competent patient continues to maintain autonomy regardless of the degree of his discomfort or the dismal prognosis.

However, if surrogates persist on continuing treatment of an incompetent patient, or disagree among themselves, I believe the physician can refuse to continue treatment on the basis of the concept of cruelty. It is indeed cruel to persist in some treatment interventions. At some point, I believe physicians can refuse further definitive treatments on the basis of cruelty, while persisting in comfort care. Should all negotiations fail, the physician can withdraw after seeking alternative care for the patient.

Of course, physicians are not obligated to discontinue treatments they feel are possibly of value unless the patient himself refuses. Nor in beginning treatments which have no biological plausibility.

On the other hand, I believe adding harmless interventions suggested by the family which do not add to discomfort of the patient may be considered, and may provide some comfort to family members. RTJ

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## **7-11 PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY VERSUS MEDICAL TREATMENT FOR NON-ACUTE CORONARY HEART DISEASE: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS**

In the past decade highly industrialized countries have seen an enormous increase in the use of percutaneous transluminal coronary angioplasty (**PTCA**) for the treatment of coronary heart disease (**CHD**). Systematic reviews have explored the effectiveness of PTCA in acute CHD as an alternative treatment to thrombolysis or as an adjuvant to thrombolysis at different times after myocardial infarction (**MI**). Few investigations have explored the effectiveness of PTCA compared with medical treatment in the management of non-acute CHD. (**NACHD**). The choice of continued medical treatment versus PTCA remains relevant for patients with limited coronary disease and good myocardial function.

This meta-analysis assessed whether PTCA is superior to medical treatment of non-acute CHD.

Conclusion: PTCA may lead to a greater reduction in angina, but at a cost of more coronary by-pass surgery. Trials have not determined estimates of the effects of PTCA on MI, death, or subsequent revascularization, though trends so far do *not* favor PTCA.

## STUDY

1. Reviewed randomized, controlled trials of patients with NACHD conducted world wide and reported between 1979 and 1998. ). NACHD includes stable angina, past history of angina, previous non-Q wave MI, and an exercise test with 3 mm ST depression.
2. In 6 trials, over 950 patients had been randomized to PTCA and over 950 to medical treatment. Three of the trials included patients with multivessel disease and pre-existing MI.

## RESULTS

1. PTCA success varied between 80% and 100%. Myocardial infarction occurred in 0.01% to 2.8%; immediate CABG in 1.5% to 2.8%. One death.
2. At the times of the studies, during PTCA only heparin was used as the antithrombotic, and stents were rarely used.
3. In all trials medical treatments included antiplatelet agents, beta-blockers, nitrates, and calcium blockers
4. PTCA was more favorable regarding subsequent angina (risk ratio 0.70 compared with medical treatment)
5. But PTCA was *less* favorable for fatal and non-fatal MI during follow-up (risk ratio = 1.42); for death (RR = 1.32); for subsequent CABG (RR = 1.59); and risk of repeat PTCA (RR = 1.29).

## DISCUSSION

1. This review suggests that PTCA may be superior to medical treatment for the alleviation of angina in patients with non-acute CHD. However, confidence intervals were wide around these pooled results, indicating considerable heterogeneity between trials.
2. Effectiveness of PTCA in relieving angina differs according to some characteristics of the patient, and the skill of the cardiologist.
3. Compared with medical treatment, PTCA may lead to an increase in CABG and is unlikely to reduce non-fatal myocardial infarction, death, or repeat PTCA
4. "The procedure should be used only in patients with non-acute CHD in whom angina cannot be controlled by medical treatment. CABG is an alternative in these patients."

## CONCLUSION

PTCA may lead to a greater reduction in angina than medical treatment in some patients with non-acute CHD. The magnitude of the effect differs according to factors the authors could not identify.

Point estimates favoring medical treatment raise the possibility that PTCA may increase MI, death, and the need for repeat PTCA, though confidence intervals do not exclude small positive treatment effects.

PTCA in these trials did increase the need for CABG.

“Clinicians should be restrained in their recommendations for PTCA, reserving the procedure for patients whose symptoms of angina are not well controlled on medical treatment.”

BMJ July 8, 2000; 321: 73-77 Meta-analysis, first author Heiner C Bucher, Medizinische Universitäts-Poliklinik, Basel Switzerland. [www.bmj.com/cgi/content/full/321/7253/71](http://www.bmj.com/cgi/content/full/321/7253/71)

Comment:

One problem with randomized trials and meta-analyses is the delay in gathering and publishing the information. At times newer techniques and medications may have been developed which would, if included in the analysis, change the conclusions.

Local experience and expertise, and the patient's self perceived degree of disability are necessary components of decision making.

This analysis is an European view. I believe in the US, patients would tilt more toward PTCA. However, medical treatment is an option in those patients for whom the risks and benefits of medical treatment and PTCA are in equipoise.

Medical treatment must be vigorous and include strict and comprehensive changes in lifestyle. (Of course, the same after PTCA.) If the patient cannot abide strict changes in lifestyle, I would tilt toward PTCA. RTJ.

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## 7-12 TREATMENT OF STABLE ANGINA

*(This editorial comments and expands on the preceding meta-analysis.)*

The treatment of stable angina aims to reduce chest pain and prevent cardiovascular events.

CABG provides a better prognosis than does medical treatment only in high risk patients with main stem disease, or 3 vessel disease.

PTCA can be performed immediately after a diagnostic procedure and is less invasive than surgery. However, it has periprocedural complications and restenosis limits its benefits in certain patients. PTCA may substantially improve quality of life, as perceived by the patient.

Beta-blockers reduce both angina and cardiac events. Aspirin, coumadin, and statins have no anti-anginal properties, but do reduce cardiac events. Medical treatment does not reverse coronary stenosis and often does not completely relieve symptoms. Only CABG and PTCA restore coronary flow.

It is likely that the true antianginal effect of PTCA is underestimated in trials because patients with severe symptoms are not randomized. Indeed, the randomization rates in most trials are quite low (around 10%). This limits the ability to generalize results of the meta-analysis.

Are these results relevant now that both PTCA (stents and glycoprotein IIb/IIIa inhibitors) and medical therapy have improved? The anti-anginal effects of PTCA are likely to be greater than in older trials. With improved materials and antithrombotic prophylaxis, complications of PTCA may be less than in the past.

The probability of plaque rupture and coronary occlusion is determined by the biological features of a lesion, and not by the degree of stenosis. Thus, treatment of a single lesion is unlikely to affect prognosis unless it is located in a proximal dominant vessel. (Ie, the main stem or left anterior descending artery.)

What is the message for primary care? In patients with severe angina, PTCA is more effective than medical treatment. However, in patients with mild angina, PTCA may not be appropriate. "We will not harm patients by using drug treatment first and using PTCA only if symptoms persist."

BMJ July 8, 2000; 321: 62-63 Editorial by Thomas F Luscher, University Hospital, Zurich, Switzerland.  
[www.bmj.com/cgi/content/full/321/7253/62](http://www.bmj.com/cgi/content/full/321/7253/62)

Comment:

Things have changed – stents, antiplatelet therapy, greater surgical experience. Better medical therapy. How now to balance them? There is a large spectrum of disease, symptoms, disability, and self-perceived quality-of life.

These are difficult choices. There are many variables. Medical vs PTCA vs CABG will depend on the severity of symptoms, the patient's preference (after being fully informed), and the experience and expertise of their cardiologists and surgeons. Patients must be informed about the track record of their physicians and surgeons and be allowed to seek out those most experienced.

Comprehensive medical therapy must continue whether or not CABG or PTCA is performed.

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**7-13 DO PATIENTS WITH SUSPECTED HEART FAILURE AND PRESERVED LEFT VENTRICULAR SYSTOLIC FUNCTION SUFFER FROM "DIASTOLIC HEART FAILURE" OR FROM MISDIAGNOSIS? A Prospective Descriptive Study**

With the recent availability of non-invasive assessment of left ventricular (**LV**) function, it is apparent that many patients diagnosed as having heart failure (**HF**) have preserved LV systolic function. It has been proposed that these patients have abnormalities of ventricular filling in diastole. The term "diastolic heart failure" has been coined.

It may be likely, given the non-specificity of the symptoms and signs used to diagnose HF, that at least some of these patients may not have abnormalities of diastolic function, but have other causes for their symptoms.

This study characterized the clinical features of patients with suspected HF but preserved LV systolic function to determine if they have other potential causes for their symptoms.

Conclusion: For most patients studied with suspected "diastolic HF", there was an alternative explanation for their symptoms

## STUDY

1. Prospective descriptive study entered 159 consecutive patients (mean age 72). All had been referred with suspected HF.
2. Patients with obvious systolic dysfunction, valvular heart disease, and atrial fibrillation were excluded.
3. Determined symptoms of shortness of breath (at rest or on exertion), paroxysmal nocturnal dyspnea, ankle swelling, and a history of coronary heart disease and chronic pulmonary disease.
4. Many had a history of hypertension or coronary disease or pulmonary disease.
5. A wide variety of cardiac and pulmonary drugs were being taken.
6. Performed echocardiography in all.

## RESULTS

1. 109 of 159 (68%; the majority women) had no evidence of LV systolic dysfunction.  
(I.e, ejection fractions were normal.)
2. Of the 109:
  - 70 had an entirely normal electrocardiogram
  - 40 were obese or very obese
  - 54 had a reduction in FEV1 < 70% of predicted normal, and peak expiratory flow rate < 70% of normal.
  - 31 had a history of angina; 12 myocardial infarction. 7 had undergone coronary artery bypass.Only 7 lacked a recognized explanation for their symptoms.

About 25% had LV hypertrophy.

## DISCUSSION

1. Many patients presenting with symptoms compatible with HF have preserved LV systolic function.
2. While these patients may have "diastolic dysfunction" as a cause of their symptoms, it is also possible that there are other explanations for their symptoms.
3. "The problem about making a diagnosis of 'diastolic heart failure' non-invasively is that there is no agreement on how this should be done, and different criteria give enormously different prevalences."
4. "Rather than examine the vexed issue of how one defines diastolic dysfunction with echocardiography, we have examined an alternative -- that is, could there be another explanation for these patients' symptoms?"
5. The most obvious alternative diagnoses are obesity, respiratory disease, and myocardial ischemia.
6. Remarkably only nine patients were of normal weight and had FEV1 greater than 70%.
7. "The important message for clinicians is that an echocardiogram suggesting diastolic dysfunction . . . is not diagnostic and represents insufficient investigation." "We clearly need to improve differentiation of breathlessness due to isolated diastolic dysfunction from that of other causes." Rigorous search for non-cardiac causes of breathlessness must be pursued.
8. Measurement of natriuretic peptides may further refine the diagnostic process.
9. What this study adds: "Improved patient care should result from recognition of the true cause of a patient's symptoms as there are appropriate management strategies for these alternative diagnoses. This is preferable to ascribing symptoms to diastolic heart failure for which there is no evidence based treatment."

## CONCLUSION

For most patients referred with a diagnosis of heart failure but with preserved left ventricular systolic function, there was an alternative explanation for their symptoms. A diagnosis of diastolic heart failure is rarely needed. These alternative diagnoses should be rigorously sought and managed.

BMJ July 22, 2000; 321: 215-18 Original investigation, first author Lynn Caruana, Western Infirmary, Glasgow, Scotland. [www.bmj.com/cgi/content/full/321/7255/215](http://www.bmj.com/cgi/content/full/321/7255/215)

Comment:

The concept, definition, and treatment of "diastolic heart failure" has escaped me over the years. I am pleased that experts also find the concept difficult. RTJ

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#### **7-14 CAN HEART FAILURE BE DIAGNOSED IN PRIMARY CARE?**

Symptomatic heart failure (**HF**) is increasingly common. It has a worse prognosis than breast cancer or prostate cancer and is second only to stroke in terms of health care costs. Morbidity from symptoms of HF is high.

Accurate and early diagnosis is important since treatment is available to reduce both morbidity and mortality, and to delay or prevent progression.

Unfortunately, HF is difficult to diagnose accurately on clinical grounds. A recent study found only about 1/4 of patients referred with suspected HF had the diagnosis confirmed by echocardiography.

"To positively establish a diagnosis of HF, most patients in primary care must be referred for cardiac imaging."

Most patients with suspected HF and preserved systolic function cannot be classed as having the elusively categorized "diastolic heart failure".

Are there alternatives to echocardiography?

A normal ECG usually excludes left ventricular dysfunction. However, changes may be subtle. Measurement of brain natriuretic peptide (**BNP**) is a potential aid to diagnosis. Data on validity are conflicting. A recent small study reported:

Sensitivity of 97%. (Ie, of 100 patients with confirmed HF, 97 had a positive BNP; 3 had a false negative test.)

Specificity of 84% (Ie, of 100 patients who did *not* have HF, 84 had a negative test; 16 had a false positive test.)

Predictive value of a positive test = 70%. (Ie, of 100 patients with a positive test — 70% true positive, 30% false positive)

Predictive value of a negative test = 98% (Ie, of 100 patients with a negative test — 98% true negative, 2% false negative.)

BNP determinations may make it easier to diagnose HF. When added to standard investigations by ECG and chest X-ray BNP may be helpful. Ie, may indicate HF when the ECG and X-ray are equivocal. The most likely initial application will be in triaging symptomatic adults to echocardiography on the basis of a positive test.

If the BNP is negative, HF is unlikely. If the BNP is positive, it may not be certain that HF is present. BNP is more effective in ruling out HF than ruling HF in. A negative test is likely to exclude HF.

## **7-15 ROLE OF EXERCISE TESTING AND SAFETY MONITORING FOR OLDER PERSONS STARTING AN EXERCISE PROGRAM.**

Benefits of physical activity and exercise among older persons are becoming increasingly clear. Physicians are being asked to help older patients (especially > 75) to start an exercise program. In those without a history of coronary heart disease, (**CHD**), how aggressively should the physician look for asymptomatic disease so that preventive and corrective measures can be taken?

This article reviews evidence supporting the benefits and risks of exercise among older persons. (*See table 2 p 344 for evidence from randomized, controlled trials supporting benefits of exercise among those > age 75*) It examines current guidelines for exercise stress testing, and offers a set of recommendations on prudent precautions that can be taken to minimize risk of adverse cardiac events among sedentary older persons in the setting of an exercise program.

The American College of Sports Medicine and the American Heart Association both recommend exercise stress testing before start of a vigorous exercise program for older sedentary persons, even in the absence of known or suspected CHD. (The distinction between moderate and vigorous exercise cannot be easily made.) The policy of routine exercise stress testing could deter many older patients who do not have CHD from starting in an exercise program. Indeed, many elderly are unable to satisfactorily complete a treadmill exercise test.

*Vigorous* exercise (6 METs or more) 3 times weekly throughout the year in persons over age 57 would slightly *increase* risk of myocardial infarction. Over time, however, regular exercise will attenuate these small elevations in absolute risk.

These authors argue that reliable implementation of guidelines in the elderly is unlikely. Guidelines have been designed primarily to address the role of exercise for developing and maintaining fitness in young and middle-aged persons, rather than restoring or enhancing physical function in older persons. The elderly differ greatly from younger persons in their high prevalence of asymptomatic CHD and the co-existence of other chronic conditions. Among cohorts of the elderly, resting ECG abnormalities are common and diminish the diagnostic accuracy of exercise treadmill testing. Given the large reservoir of asymptomatic CHD among older persons, routine exercise testing would likely lead to a cascade of invasive cardiac procedures along with unnecessary iatrogenic complications.

The authors argue that routine exercise stress testing at the beginning of an exercise program in the elderly would be expensive and might cause more harm than good.

So, what should we recommend?

The author's recommendations are based on over 30 years of accumulated experience working with older persons in clinical and research centers. Before starting a program:

1. History and physical to identify potential cardiac contraindications to exercise outside a monitored environment: myocardial infarction within 6 months., angina, signs of heart failure, systolic BP > 200, diastolic > 110.
2. Simple tests of cardiac reserve: getting up and down from the examining table, walking 15 meters, climbing 1 flight of steps. Those with chest pain or substantial shortness of breath would not be good candidates.
3. Review resting ECG. Persons with overt changes should be risk stratified and managed accordingly.
4. Consider co-existing conditions such as musculoskeletal disorders and neurological conditions.

All previously sedentary elderly persons without overt cardiovascular disease should start with a low-intensity exercise program: gait and balance exercises, tai chi, self-paced walking, lower extremity resistance training. Intensity and amount of exercise should be gradually increased.

Those who have an abnormal cardiac response (decrease in systolic BP > 20 mm Hg, or increase of systolic BP to over 200, heart rate increase > 90% of age-specific maximum) are poor candidates for moderate exercise and should be advised to continue with less intensive exercise.

Current guidelines regarding exercise stress testing are not applicable for the vast majority of older persons who are interested in restoring or enhancing their physical function through a program of physical activity and exercise. The goal should be not to deter older persons from participating, but to take prudent precautions. "Relatively few persons aged 75 and older are capable of participating in vigorous or high intensity aerobic training."

JAMA July 19, 2000; 284: 342-49 "Special Communication", first author Thomas M Gill, Yale University School of Medicine, New Haven, Conn. [www.jama.com](http://www.jama.com)

Comment:

Primary care clinicians should use their common sense, rather than automatically advising high-tech testing for the many elderly who would benefit from increasing their physical activity by a structured program. RTJ

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## **7-16 RANDOMISED TRIAL OF EFFECTS OF CALCIUM ANTAGONISTS COMPARED WITH DIURETICS AND BETA-BLOCKERS ON CARDIOVASCULAR MORBIDITY AND MORTALITY IN HYPERTENSION: The Nordic Diltiazem (NORDIL) Study**

No randomized trials have shown that antihypertensive treatment with calcium antagonists (CAs) decrease cardiovascular morbidity and mortality. Diuretics and beta-blockers have been shown to do so.

CAs have been used extensively for treatment of hypertension. Some authorities consider them first-line therapy.

This trial, begun in 1992, compared effects of 1) diltiazem (a non-dihydropyridine CA) with that of 2) diuretics, beta-blockers, or both, on cardiovascular morbidity and mortality in middle-aged patients with hypertension.

Conclusion: The two regimens were equally effective.

### STUDY

1. Multicenter, prospective, randomized trial entered over 10 500 patients with hypertension (age 50-69). All had diastolic BP over 100 mm Hg. Mean BP = 173/106
2. Randomized to:
  - 1) Diltiazem, 180-360 mg daily. For step 2, an ACE inhibitor was added
  - 2) Beta-blocker, or diuretic. For step 2, both could be used together.
3. Follow-up = 5 years.

### RESULTS

1. Mean BP during the study: diltiazem group = 155/89; diuretic, beta-blocker group = 152/89. In both groups, BP was lowered effectively, systolic BP lowered somewhat more in the diuretic-beta-blocker group (23 mm vs 20 mm).
2. At the end of the trial, 50% of all patients in the diltiazem group were still taking diltiazem as monotherapy, compared with 45% on the diuretic-beta-blocker group.
3. Combined primary endpoint ( fatal and non-fatal stroke, myocardial infarction and other cardiovascular death) occurred equally in the 2 groups (16.6 events per 100 patient-years vs 16.2 per 1000 patient-years.)
4. Fatal and non-fatal stroke occurred more commonly in the diuretic beta-blocker group. (7.9 events per 1000 patient-years vs 6.4)
5. Fatal and non-fatal myocardial infarction occurred more commonly in the diltiazem group.

(7.4 vs 6.3 events per 1000 patient-years.)

6. The 2 regimens were equally well tolerated.

## CONCLUSION

Two regimens, one based on the calcium antagonist diltiazem and the other on diuretics, beta-blockers, or both, were equally effective in preventing a combined endpoint of stroke, myocardial infarction, and cardiovascular death over 5 years.

Lancet July 29, 2000; 356: 359-65 Original investigation by the NORDIL Study Group, first author Lennart Hansson, University of Uppsala, Sweden. [www.thelancet.com](http://www.thelancet.com)

Comment:

This was a large, expensive multicenter, trial done in Norway and Sweden. Clinicians who prefer a diuretic based treatment plan may take comfort. Clinicians who favor diltiazem may take comfort as well. The study favored neither. The title of the study may have been too inclusive. Only one calcium blocker (diltiazem) was tested.

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## **7-17 MORBIDITY AND MORTALITY IN PATIENTS RANDOMISED TO DOUBLE-BLIND TREATMENT WITH A LONG-ACTING CALCIUM-CHANNEL BLOCKER OR DIURETIC IN THE INTERNATIONAL NIFEDIPINE GITS STUDY: INTERVENTION AS A GOAL IN HYPERTENSION TREATMENT (INSIGHT)"**

This study complements the preceding. Diuretic based therapy was just as effective and safe as calcium-blocker therapy.

Lancet July 29, 2000; 356: 366-72 Original investigation, first author Morris J Brown, University of Cambridge, UK [www.thelancet.com](http://www.thelancet.com)

Comment:

These two studies go a long way to dispel the recent negative comments about safety of calcium blockers. However, note that the diuretic/amiloride combination was just as effective and much less expensive.

COST?

My pharmacy quotes:

Amiloride 5 mg/hydrochlorothiazide 50 mg -- \$8.18 for 100. Splitting the tablet will reduce the cost to about \$4 for 3 months supply, or about 1\$ per month

Nifedipine extended release 30 mg -- \$114 for 100 tablets or about \$35 per month. RTJ

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## **7-18 DIFFERENCES BETWEEN BLOOD-PRESSURE-LOWERING DRUGS**

( *This editorial comments and expands on the preceding studies.*)

Until recently, evidence about effects of BP-lowering drugs on the risks of major cardiovascular diseases came mostly from trials of diuretic and beta-blocker based regimens. The trials showed a reduction in risk of stroke by about 38%, of coronary heart disease of 16%, and of congestive heart failure by 40%.

More recently, trials of calcium-channel blockers and ACE inhibitors indicated that benefits of BP-lowering drugs are not restricted to diuretics or beta-blockers.

However, doubt still exists about whether there are any important differences in the size of benefits.

The preceding 2 trials demonstrated *no difference* in outcomes between diuretic/beta-blocker based regimens and calcium channel blocker based regimens. Any differences were of marginal significance.

What to conclude? We still do not know if there is any greater benefit from one regimen or another. Both resulted in equal benefits.

Lancet July 29,2000; 356: 352-53 Editorial by Stephen MacMahon and Bruce Neal, University of Sydney, Australia. [www.thelancet.com](http://www.thelancet.com)

Comment:

These studies provide some comfort for those who prescribe and those who take calcium-channel-blockers. The flurry of excitement due to reported adverse effects of channel blockers, especially the short-acting variety has abated.

Treatment of hypertension lasts for years. Costs are therefore high. I would start treatment with the least expensive regimen (generic hydrochlorothiazide and generic amiloride). And add generic atenolol (a beta-blocker) if needed. Cost of the 3 combined generic drugs would be about \$3 to \$4 a month. RTJ

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## RECOMMENDED READING

### **7-19 ENVIRONMENTAL AND HERITABLE FACTORS IN THE CAUSATION OF CANCER Analysis Of Cohorts Of Twins From Sweden, Denmark, And Finland**

Studies of twins make it possible to estimate the overall contribution of genes to the development of malignant diseases.

This study combined data from over 44 000 pairs of twins. It estimated the risks of cancer at 28 anatomical sites in which one of the twins had cancer. Used statistical modeling to estimate the importance of heritable and environmental causes of cancer at 11 sites. (*Table 2 pp 80-81*)

The study concerned twins of the same sex who could be mono-zygotic (who share all genes) or di-zygotic (who, on average, share 50% of genes). If studies of twins show that concordance of cancer is higher in mono-zygotic twins than among di-zygotic twins, genetic factors are likely to be important.

Results: Cancer occurred in over 10 000 persons among over 9000 pairs of twins. An increased risk was found among the twin of the affected twin for stomach, colorectal, lung, breast, and prostate cancer. Statistically significant effects of heritable factors were observed for:

Prostate cancer (42% of risk may be explained by heredity)

Colorectal cancer (35%)

Breast cancer (27%)

Even though the study found familial (hereditary and non-hereditary) effects for cancer at many sites, the rates of concordance in twins were generally below 10%. “This result indicates that, for nearly all sites, the twin of a second twin with cancer has only a moderate absolute risk of having cancer at the same site.” The absolute risk of the same cancer before age 75 for the mono-zygotic twin of the other twin with colorectal, breast or prostate cancer was between 11% and 18%. For di-zygotic twins, the risk was 3% to 9%.

For non-shared environmental factors (any unique environmental cause of cancer that is not inherited and not shared between twins) the contribution ranged from 58% to 82%.

“We conclude that the overwhelming contributor to the causation of cancer in the population of twins that we studied was the environment.” Environment has the principal role in causing sporadic cancer.

Relatively large heritable proportions of cancer at some sites suggest major gaps in our understanding of heritable cancer. Even for cancers for which there is statistically significant evidence of a heritable component, most pairs of twins were discordant for that cancer. “On the population level, the increase in the risk of cancer even among close relatives of affected persons is generally moderate.”

NEJM July 13, 2000; 343: 78-85 Original investigation, first author Paul Lichtenstein, Karolinska Institute, Stockholm, Sweden [www.nejm.com](http://www.nejm.com)

An editorial in this issue (*pp 135-36*) comments further:

Geographic differences, trends over time in the risk of cancer, and detailed studies of migrant populations overwhelmingly implicate environmental exposures as major causal factors, and often identify the responsible carcinogens (eg, tobacco, alcohol, radiation, occupational toxins, infections, diet, drugs). This has led to the widely accepted estimate that 80 to 90 percent of human cancer is due to environmental factors.

Yet, in the past 15 years, the explosion of molecular genetics has overshadowed environmental explanations by revealing genetic mechanisms underlying cancer. This causes confusion about risk of cancer among families, clinicians, researchers, public policy makers, and the general public.

There is a low probability that a same-type cancer will develop in a person whose identical twin has that type of cancer. Consider that a woman’s average annual risk of a contralateral breast cancer after the

diagnosis of a first primary breast cancer is less than 1%. This is the risk for a person with , obviously, not only the identical genome, but also the identical complex of exposures.

Comment:

What is the clinical application? This should bring some reassurance to family members. I would still consider screening family members for breast, prostate, and colo-rectal cancer. RTJ

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### *The Cutting Edge*

#### **7-20 INTRAVENOUS NESIRITIDE: A Natriuretic Peptide In The Treatment Of Decompensated Congestive Heart Failure.**

Symptomatic decompensation is the most common reason for hospitalization of patients with congestive heart failure (**CHF**) due to left ventricular systolic dysfunction. Dyspnea and fatigue are associated with pulmonary congestion and low cardiac output.

Brain (B type) natriuretic peptide is synthesized normally in the ventricular myocardium in response to the ventricular stretch or increased pressure which occurs in CHF. It is a normally produced hormone that acts to reduce some of the adverse effects of CHF. It induces arterial and venous dilation, enhances sodium excretion, and depresses the renin-angiotensin-aldosterone system as well as the sympathetic nervous system.

Now brain natriuretic peptide can be produced by recombinant technology. (Nesiritide; *Natrecor* )

This study investigated the clinical usefulness of nesiritide in treatment of CHF.

Conclusion: Nesiritide improved hemodynamic function and clinical status in the short-term.

#### **STUDY**

1. The study was conducted in 2 parts. All patients were hospitalized because of symptomatic CHF.

A. Efficacy trial entered 127 patients with CHF.

All received placement of a Swan-Ganz catheter.

All had a pulmonary capillary wedge pressure of 18 mm Hg or more and a cardiac index of 2.7 liters or less per minute per square meter of body surface.

Assigned double-blind to treatment with iv nesiritide or placebo for 6 hours.

B. Comparative trial entered 305 patients with CHF

None received hemodynamic monitoring.

Randomly assigned to open label therapy with standard agents or continuous iv nesiritide.

Duration = 7 days.

## RESULTS

### 1. Efficacy trial:

A. At 6 hours	Nesiritide	Placebo
Pulmonary capillary wedge pressure	-10 mm	+ 2mm
Improved global clinical status	67% of patients	14% of patients
Dyspnea improvement	53% of patients	12% of patients
Reduced fatigue	38% of patients	5% of patients

Systemic vascular resistance decreased and cardiac index increased in the active treatment group.

### 2. Comparative trial:

The improvements in global clinical status, dyspnea, and fatigue were sustained to a similar degree for up to 7 days.

(Note that the drug was given iv continuously over the 7 days.)

### 3. Side effects: The most common was hypotension, usually asymptomatic.

## DISCUSSION

1. Infusion of nesiritide in patients admitted to the hospital specifically for management of decompensated CHF resulted in improvements in hemodynamic function, and rapid and sustained improvements in clinical status.
2. The study population was specifically selected to represent patients in whom rapid symptomatic and hemodynamic effects were desired.
3. The plasma levels of naturally occurring brain natriuretic were elevated at baseline, indicating severity of the decompensation. (Ie, the drug treatment consisted of addition of therapeutic brain natriuretic peptide.)
4. Since nesiritide exerts *no* direct positive inotropic effect, on the myocardium, the increase in cardiac output presumably reflects a reduction in left ventricular afterload.
5. The decrease in BP was not associated with any reflex tachycardia or increase in plasma norepinephrine.
6. Urine output increased in a dose-dependent manner. The effects of the drug are also consistent with a direct renal effect.

## CONCLUSION

In patients hospitalized for treatment of decompensated CHF, nesiritide improved hemodynamic function and clinical status. "Intravenous nesiritide is useful for the short-term treatment of decompensated congestive heart failure."

NEJM July 27, 2000; 343; 246-53 Original investigation by the Nesiritide Study Group, first author, Wilson S Colucci, Boston University Medical Center, Boston, Mass. [www.nejm.com](http://www.nejm.com)

Comment:

An unusual number of effective drugs have been added to the treatment of CHF over the past few years. This is the first I have encountered using natriuretic peptide for treatment (rather than for diagnosis). Sorting out the most effective regime(s) will require much more long-term study. The best combination will require individualization.

Not a practical point at this time, but it was provocative enough to include.

Prevention is still the goal. Treatment will remain a rear-guard action and the prognosis poor. RTJ

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## **7-21 DDT HOUSE SPRAYING AND RE-EMERGING MALARIA**

"Globally, numbers of malaria cases are increasing and the rate of increase is accelerating." Malaria is reappearing in urban areas and in countries that previously eradicated the disease. The frequency of imported malaria has increased in USA and Europe.

"Although many factors contribute to increasing malaria, the strongest correlation is with the decreasing numbers of houses sprayed with DDT" Recognition of this link and the start of negotiations by the United Nations Environment Program for global elimination of DDT has fueled an intense debate. Many in the scientific community support the continued use of DDT for spraying houses for malaria control. "When DDT was sprayed on house walls, it exerted powerful control over indoor transmission of malaria."

The overall effect of structured programs for applying DDT to house walls was an almost complete reduction or elimination of malaria. When a malaria-endemic country stops using DDT, there is a cessation or great reduction in numbers of houses sprayed accompanied by rapid growth of malaria burden within the country.

Resistance of *Anopheles* mosquitoes to DDT is not a major barrier to the continued use of DDT for malaria control. (Where DDT is still effective it should be used.)

Claims of risk of DDT to human health have not been confirmed. It has been used for malaria control for almost 55 years. But since the 1970s, DDT has been banned in industrialized countries (and the ban has been gradually extended to malarious countries) because of environmental concerns. The WHO's malaria control strategies have promoted a move away from spraying houses. "These strategies were adopted even though published WHO documents and committee reports have consistently and accurately characterized DDT-sprayed houses as the most cost effective and safest approach to malaria control."

On a landscape scale, a sprayed house will only have a very small amount of DDT enclosed in the walls. But, some environmentalists have argued that if DDT is produced for use in improving public health, it will also be used for agriculture and lead to global pollution of the environment.

In the 1980s numerous epidemics of malaria occurred in many countries following suspension of DDT. Over 100 000 persons were killed. Authorities in some countries restarted DDT house spraying and stopped the catastrophic epidemics. In Madagascar, malaria incidence declined more than 90% just after 2 annual spray cycles.

There is no ideal solution to malaria control. DDT house spraying has its limitations. "However, DDT remains a remarkably effective tool that should be used."

Concerns about adverse environmental effects could be lessened by use of wall spray (2 g/m<sup>2</sup>) once a year instead of every six months, use in designated rooms of the house, and use in designated areas. "We recommend that the global response to burgeoning malaria rates should allow for DDT residual house spraying where it is known to be effective and necessary." One organization should be created to manufacture and distribute DDT to public-health organizations in countries that need it. This would guarantee use for public-health purposes only. The necessary quantity of DDT for vector control will be so low that, even if diverted, it will not be enough to pollute the environment.

Lancet July 22, 2000; 356: 33032 "Viewpoint", editorial, first author D R Roberts, Uniformed Services University of Health Sciences, Bethesda, Maryland. [www.thelancet.com](http://www.thelancet.com)

Comment:

This reminded me of the conflict regarding use of antibiotics — possible benefit to the individual balanced against an adverse effect on the community. If I lived in an endemic area, I would want my house sprayed. I would not believe this would have any significant deleterious effect on the environment.

RTJ

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## REFERENCE ARTICLE

### 7-22 HYPERTENSIVE EMERGENCIES

*Hypertensive emergency* — a situation in which uncontrolled hypertension is associated with acute end-organ damage. Reduction (not necessarily to normal values) is required to prevent or limit target-organ damage. Examples – encephalopathy and aortic dissection which require emergency BP reduction with intensive monitoring and parenteral drug therapy. (Eg, sodium nitroprusside, beta-blockers, labetalol, calcium-channel blockers. . Short term anticonvulsants can be used for associated seizures.

*Hypertensive urgency* – a situation in which BP should be lowered within a few hours (ie, requires urgent, but not emergency BP reduction).

The distinction is important because it dictates management.

Most patients with hypertensive emergencies have chronic hypertension, although it may occur in previously normotensive persons, particularly when associated with pre-eclampsia and acute glomerulonephritis.

The review discusses epidemiology, etiology, pathophysiology, clinical evaluation, hypertensive encephalopathy, and management. (*See table 2 p 415, for commonly used parenteral antihypertensive drugs.*)

The use of antihypertensive therapy in cerebral ischemic syndromes, in contrast to hypertensive encephalopathy is controversial. In many patients with acute ischemic stroke BP is raised; and cerebral autoregulation may fail. Areas around the stroke infarct become even more prone to hypoperfusion. There is evidence of better outcomes in patients with acute stroke who have higher BP . Thus, antihypertensive therapy is not routinely recommended.

Lancet July 29, 2000; 356: 411-17 “Seminar” review article by Carl J Vaughan Weill Medical College of Cornell University, New York, and Norman Delanty Royal College of Surgeons in Ireland, Dublin  
[www.thelancet.com](http://www.thelancet.com)

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## REFERENCE ARTICLE

### 7-23 DRUG THERAPY FOR BREAST-FEEDING WOMEN

Analysis of the risks of an infant’s exposure to a drug excreted in breast milk needs to take into account the answers to two key questions: 1) How much of the drug is excreted in milk?, and 2) At this level of excretion, what is the adverse effect?

There is little epidemiological data regarding the risk of adverse effects in infants as a result of exposure to drugs in breast milk. Available studies suggest that clinically important effects are rare, although about 1 in 10 of the mothers noted their infants had minor effects that did not require medical attention. “In most cases the paucity of the data precludes a comparison of the risks of exposure with the disadvantages of discontinuing breast feeding.”

The article summarizes the current knowledge about some of the drugs and non-medical compounds which warrants a more detailed assessment of risk. (*These are listed in table 1, p 120. Drugs of choice in table2, p 124*)

Most drugs taken by nursing mothers are excreted in breast milk, but the risk to their infants seems limited. The exceptions are the drugs that result in high levels of exposure in the infants and those with substantial adverse effects on the infants. Unfortunately information about this is scarce.

NEJM July 13, 2000; 343: 118-126 “Drug Therapy” review article by Shinya Ito, University of Toronto, Canada. [www.nejm.com](http://www.nejm.com)

Comment:

More important would be drug taking during pregnancy, especially early pregnancy.

The issue before primary care clinicians (as well as pediatricians) relates to drug prescriptions for patients who are breast-feeding. Clinicians must use caution and give their breast-feeding patients best available information. This review and the PDR may help. Drugs having anti-folate properties, given in early pregnancy, are reported to produce congenital defects.

The issue of alternative medicines must also be addressed.

Can small doses of drugs in milk induce allergy in infants? RTJ

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### RECOMMENDED READING

#### **7-24 PROFESSIONALISM: An Ideal To Be Sustained**

“The core elements of a profession are possession of a specialized body of knowledge and commitment to service.”

“A gulf has developed between the medical profession and the society it serves. As one observer noted, “A better informed community is asking for accountability, transparency, and sound professional standards” whereas medicine feels that “the professional’s autonomy is severely restricted by budgets, bureaucracy, guidelines, and peer review”. The concept of professionalism bridges the interests of physicians and society. Society’s need for the healer and its belief in the inherent value and morality of professionalism have served as the basis of modern medicine. They are the source of the rights and privileges granted to the medical profession and of the values that physicians feel contribute to what is noble and good in their calling. Recently, a series of highly publicized events has encouraged the view that the medical profession fails to meet many of the obligations required to sustain its professionalism.”

“A redefinition of expectations and roles is taking place. To prevent medicine from becoming a commodity in a market-oriented world, physicians must participate in shaping the profession’s future, and understand the principles and obligations associated with being a member of a profession.”

“As medicine negotiates a new understanding with society, the preservation of the ideals of professionalism, which serves as the basis of trust, is of great importance. Professionals should show that professionalism is a benefit to society. For this to occur, they should meet their obligations. The stakes are high, as adequate health care for the public is inconceivable without a committed profession, and physicians cannot function effectively as healers without the trust of the patient and society.”

Lancet July 8, 2000; 356: 156-59 "Viewpoint", editorial, first author Richard L Cruess, McGill University, Quebec, Canada. [www.thelancet.com](http://www.thelancet.com)

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## **7-25 NINE PRINCIPLES OF FAMILY MEDICINE**

- (1) Family physicians are committed to the person rather than to a particular body of knowledge.**
- (2) Seek to understand the context of the illness.**
- (3) See every contact with their patient as an opportunity for prevention or health education.**
- (4) View the patients in their practice as a population at risk.**
- (5) See themselves as part of a community-wide network of supportive and healthcare agencies.**
- (6) Should ideally share the same habitat as their patients**
- (7) See patients in their homes.**
- (8) Attach importance to the subjective aspects of medicine,**
- (9) Manage resources.**

BMJ July 15, 2000; 321: 173 Quote from McWhinney I "*A Textbook of Family Medicine*" Oxford University Press, 1997 A box in letters to the editor "Is it time for a new definition of general practice"

BMJ July 15, 2000; 173-74 <http://www.bmj.com/cgi/content/full/321/7254/173>

Comment:

A tall order! Primary care and family medicine are the most complex and difficult of specialties.

Worth framing and placing on the office wall. RTJ



