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HIGHLIGHTS JANUARY 2000

1-1 THE RELATION BETWEEN BLOOD PRESSURE AND MORTALITY DUE TO CORONARY HEART DISEASE AMONG MEN IN DIFFERENT PARTS OF THE WORLD.

1) Absolute risk of mortality from CHD at a given BP differed significantly between countries. 2) In all countries, absolute risk also rose with each quartile of increase in BP. 3) There was no distinct cutpoint below which risk did not continue to decline or above which risk did not increase. 4) At a given BP (eg, 140/80) absolute risks differed between populations by a factor of 3 to 4.

If the absolute risk of CHD is taken as a criterion for the use of antihypertensive therapy, this finding will have major implications for clinical practice in different parts of the world. Treatment of BP should be based on absolute risk of CHD in each individual, not on the level of BP. *NEJM* January 6, 2000; 342: 1-8

1-2 BLOOD PRESSURE AND THE RISK OF CARDIOVASCULAR DISEASE.

Prognosis among persons with "hypertension" is highly variable, depending on factors other than BP — sex, age, other risk factors, target organ damage, and history of cardiovascular disease.

"The usefulness of hypertension as an independent diagnostic category appears to be limited and it is arguable, from both a public health and clinical perspective, that we should refocus our efforts toward the lowering of blood pressure and the prevention of blood-pressure-related diseases, in both hypertensive and *nonhypertensive* persons. (Ie, in some individuals lowering BP from 140/85 to 125/80 may be more beneficial than lowering BP from 160/95 to 140/90.

"There is clearly a strong rationale for expecting many patients who are at high risk for major cardiovascular events (whether they are 'hypertensive' or not) to benefit from a substantive reduction in blood pressure." *NEJM* January 6,2000; 342: 50-52

1- 3 EFFECTS OF AN ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

The ACE inhibitor ramipril reduced rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who were not known to have a low ejection fraction or heart failure *NEJM* January 20, 2000;342: 145-53

1-4 ACE INHIBITION IN CARDIOVASCULAR DISEASE

"It is reasonable to prescribe ramipril for patients who are similar to those enrolled in the HOPE study – high-risk patients with a history of coronary disease, peripheral vascular disease, stroke, or diabetes mellitus and at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol levels, cigarette smoking, or documented microalbuminuria." This will greatly broaden the spectrum of patients who can be treated effectively. *NEJM* January 20, 2000;342:201-02

1-5 EFFECT OF RAMIPRIL ON CARDIOVASCULAR AND MICROVASCULAR OUTCOMES IN PEOPLE WITH DIABETES MELLIUS: Results of the HOPE Study and MICRO-HOPE Study

Ramipril was beneficial in reducing cardiovascular events and overt nephropathy in persons with diabetes. Benefit was greater than that attributable to decrease in BP. This treatment represents a vasculoprotective and renoprotective effect. *Lancet* January 22, 2000; 355: 253-59

1-6 HOPE AND EXTENSION OF THE INDICATIONS FOR ACE INHIBITORS?

These findings have considerable implications for clinical practice. They indicate that virtually *all* patients with a history of cardiovascular disease, not just those with an acute myocardial infarction or heart failure, may benefit from ACE inhibition.

Patients in the study were on maximum therapy for major risk factors, including hypertension. The observed benefit of ramipril was *in addition* to the drugs many subjects were already taking (beta-blockers, calcium blockers, diuretics, aspirin, and lipid-controlling agents). *Lancet* January 22, 2000; 355: 246-47

1-7 VITAMIN E SUPPLEMENTATION AND CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

Vitamin E, in this cohort of high-risk patients, had no apparent benefit on cardiovascular outcomes. It is very unlikely that vitamin E given for 5 years has any clinically worthwhile effect on cardiovascular disease. *NEJM* January 20,2000;342: 154-60

1-8 PENICILLIN FOR ACUTE SORE THROAT: Randomised Double Blind Trial of Seven Days Versus Three Days Treatment or Placebo in Adults.

A seven day course of penicillin was effective in reducing duration of symptoms and reducing risk of suppurative complications. It is also effective in non-group A infections and reduced the risk of recurrent sore throat over the next 6 months.

A 3-day course was not any more effective than placebo in reducing total days of symptoms. *BMJ* January 15, 2000; 320: 150-154

1-9 SORE THROATS AND ANTIBIOTICS

"There is no single course of action that will suit all, or even most, patients." The evidence must be applied in different ways according to local conditions. These will include environmental factors (places in the world

where acute rheumatic fever is common), history (previous middle ear infection), and social factors. "General practitioners put as much weight on social factors as on the physical examination in deciding whether or not to use antibiotics. Both patients and their doctors dance delicately around the complicated negotiation of antibiotics for upper respiratory infections, each aware of the other's sensibilities."

"At some point the benefits and harms resulting from treatments, . . . including emerging antibiotic resistance and costs to society, are so finely balanced that patients and their doctors must decide on a choice that is likely to be tipped one way by personal preference alone."

"To expect a one line answer from the evidence (a guideline, for example) is to ask too much." *BMJ* January 15,2000; 320: 130-31

1-10 MENOPAUSAL ESTROGEN AND ESTROGEN-PROGESTIN REPLACEMENT THERAPY AND BREAST CANCER RISK

Hormone replacement therapy with estrogen-progestin increased risk of breast cancer beyond that of estrogen alone. *JAMA* January 26, 2000; 283; 485-491

1-11 POSTMENOPAUSAL ESTROGENS – OPPPOSED, UNOPPOSED, OR NONE OF THE ABOVE

The risks of BC due to HT use are determined by duration of use. Short-term use (eg, 2 to 3 years) for relief of menopausal symptoms should not be influenced by fear of BC.

The editorialist tilts toward lifestyle measures as first line therapy, and suggests this may be all that is needed to preserve bone mass. This begs the question — will drug therapy add to the benefits of a high-quality and sustained lifestyle? *JAMA* January 26, 2000; 283: 534-35

1-12 RISK ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN PRIMARY CARE: Cross Sectional Study Evaluating A Range of Diagnostic Tests

A normal electrocardiogram implies a low risk of left ventricular systolic dysfunction. An abnormal ECG combined with either a high atrial natriuretic peptide or a resting heart rate greater than diastolic BP, or both, identified patients with left ventricular systolic dysfunction. *BMJ* January 22, 2000;320:220-24

1-13 EFFECTS OF INFLUENZA VACCINATION OF HEALTH-CARE WORKERS ON MORTALITY OF ELDERLY PEOPLE IN LONG-TERM CARE

Vaccination of health-care workers was associated with a substantial decrease in mortality among frail elderly patients in hospitals. *Lancet* January 8, 2000; 355: 93-97

1-14 URINARY AND SEXUAL FUNCTION AFTER RADICAL PROSTATECTOMY FOR CLINICALLY LOCALIZED PROSTATE CANCER.

Radical prostatectomy was associated with significant erectile dysfunction and some decline in urinary function. *JAMA* January 19,2000;283: 354-60

1-15 THE VALUE OF PREOPERATIVE MEDICAL TESTING BEFORE CATARACT SURGERY

Routine medical testing before cataract surgery did not increase the safety of the surgery. *NEJM* January 20,2000;342:168-75

1-16 POTENTIAL RISK OF CROSS-INFECTION DURING PERIPHERAL-VENOUS ACCESS BY CONTAMINATION OF TOURNIQUETS

Many tourniquets were contaminated with blood. On culture, a high percentage grew out pathogenic bacteria.

This presents a risk of transmission of bacterial as well as viral infections. "We recommend the use of disposable tourniquets." *Lancet* January 1, 2000; 355:44

1-17 ORAL MONTELUKAST COMPARED WITH INHALED SALMETEROL TO PREVENT EXERCISE-INDUCED BRONCHOCONSTRICTION

The bronchoprotective effects of montelukast against exercise-induced bronchoconstriction were maintained throughout 8 weeks. Salmeterol lost much of its benefit over the same time. Tolerance developed to salmeterol, but not to montelukast. *Annals Int Med* January 18, 2000; 132: 97-104

1-18 45-YEAR FOLLOW-UP OF HEPATITIS C INFECTION IN HEALTHY YOUNG ADULTS

Over 45 years 17 HCV positive persons had a low liver-disease related morbidity and mortality. Only 2 (12%) developed liver disease. "This suggests that healthy HCV-positive persons may be at less risk for progressive liver disease than is currently thought." *Annals Int Med* January 18, 2000; 132: 105- 11

1-19 HERB-DRUG INTERACTIONS

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. However, many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspect preparations. Health-care practitioners should caution patients about mixing herbs and pharmaceutical drugs. *Lancet* January 8, 2000;355:134-38

1-20 TREATMENT OF ALZHEIMER'S DISEASE

Review of criteria for diagnosis, outcome measures in clinical trials, cholinergic augmentation therapy, treatment of behavioral manifestations, *NEJM* November 25, 1999; 341: 1670-1679

1-21 LOOKING BACK ON THE MILLENNIUM IN MEDICINE

The editors of NEJM choose the most important developments in clinical medicine over the past millennium — 11 in all. Which ones would you choose? *NEJM* January 6, 2000; 42-49

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1-1 THE RELATION BETWEEN BLOOD PRESSURE AND MORTALITY DUE TO CORONARY HEART DISEASE AMONG MEN IN DIFFERENT PARTS OF THE WORLD.

This remarkable 25-year observational study is a continuation of the famous "Seven Countries" work reported by Dr. Keys in 1966. His epidemiological studies laid the groundwork for much of our understanding about the relations between cholesterol and coronary heart disease.

The present study compared risk of death from coronary heart disease (**CHD**) in various populations as related to BP.

It presents absolute differences in mortality as well as relative differences.

Conclusions: 1) Absolute risk of mortality from CHD at a given BP differed significantly between countries. 2) In all countries, absolute risk also rose with each quartile of increase in BP. 3) There was no distinct cutpoint below which risk did not continue to decline or above which risk did not increase. 4) At a given BP (eg, 140/80) absolute risks differed between populations by a factor of 3 to 4.

STUDY

1. Examined six populations in different parts of the world (USA, Northern Europe, Mediterranean Europe, Inland Southern Europe, Serbia, and Japan).
2. Entered over 12 000 men (age range 40 to 59). All were free of CHD at baseline. Measured BP at baseline (1958 to 1964). Repeated BP measurements over the next 5 years.
3. Followed for 25 years. Only 54 were lost to follow-up. End-point = death from CHD

RESULTS

1. Average mean BP at baseline varied between countries:

   Systolic from 132 in Serbia to 144 in Northern Europe

   Diastolic from 76 in Japan to 87 in Northern and Inland Southern Europe.

   (Why is mean BP lower in some areas?)

2. Age standardized 25 year mortality from CHD: (Number per 10 000 person-years)

Japan —	17
Mediterranean Europe —	22
Serbia —	41
Inland Southern Europe —	46
United States —	73
Northern Europe —	100

   (Why does mortality vary so much between countries?)

3. The *absolute* risk of death from CHD at a *given value of BP* varied considerably:

   For a usual systolic BP of about 140:

   Japan and Mediterranean Europe — 20 per 10 000 person years.

   Northern Europe and US — 70 per 10 000 person-years.

   (Why, for a given BP does prognosis vary so much?)

   For a usual diastolic BP of about 85, a similar pattern of variation risk was observed.

4. Prevalence of "hypertension" (defined as ≥160; ≥ 95, or ≥160/95) varied considerably:

   Serbia and Japan — 16%

   Northern Europe — 30%

   (Why does the prevalence of "hypertension" vary?)

5. "Hypertension" (≥ 160/95) was a significant risk factor in all 6 populations, but the absolute risk of death from CHD associated with "hypertension" was clearly different between populations — from 44 per 10 000 person-years in Japan and Mediterranean Europe to 153 per 10 000 person-years in Northern Europe and 116 in the US.

6. Absolute mortality from CHD rose with each quartile of systolic and diastolic BP in most populations.
   (*See figures 1 and 2 pp 3 and 4*)

   A. In the US:

   Systolic BP (*my estimates from the figure RTJ*)

	Mortality from CHD (No. per 10 000 person-years
1st quartile = 120	41
2nd quartile = 130	42
3rd quartile = 140	75
4th quartile = 160	100

   B. In Northern Europe (Note, no distinct cut-point)

1st quartile = 125	50
2nd quartile = 135	70
3rd quartile = 145	75
4th quartile = 160	130

7. Similar increases in mortality occurred with each quartile increase in diastolic BP. (Ie, mortality increased as BP increased within the range of diastolic BP usually considered "normal".)

DISCUSSION

1. The absolute risk of death from CHD varied considerably between populations.
2. When "hypertension" was defined as ≥140/90, the relative risk of death from CHD was 1.5 when compared with those with lower BP.
3. At a given BP (eg, 140/90) there was a considerable difference in risk between populations. (From 20 per 10 000 person-years in Mediterranean area to 70 in Northern Europe.) These differences cannot be explained by differences in age or smoking prevalence. (The Seven Countries Study found similar heterogeneity in cholesterol levels.)
4. The investigators suggest several possible reasons for the heterogeneity: genetic differences; nutritional factors and dietary patterns (less meat and more olive oil, fish, fruit, vegetables, and alcohol in the Mediterranean). In Finland, a decrease in mortality from CHD occurred between 1972 and 1992 which corresponded to a substantial increase in consumption of fruits and vegetables.
5. The large difference between the risk of CHD in the US and northern Europe compared with Japan

and Mediterranean southern Europe *at the same BP* may have important implications for treatment. A recent European task force recommended use of the absolute risk of CHD, based on all the major risk factors, as a criterion for starting drug treatment for BP. Individuals whose absolute multifactorial risk of CHD exceeds 20% over the next 10 years or exceeds 20% if projected to age 60, have a sufficiently high risk to justify the selective use of proven drug therapies. The results of the Seven Countries Study imply that, at the same BP, this criterion will be met at lower blood pressures in the US and northern Europe than in Japan and Mediterranean southern Europe.

6. "Of course, the decision to start drug treatment is not based solely on absolute risk. Other factors, such as clinical history, age, and sex of the patient and the cost effectiveness of the therapy are also important."

CONCLUSION

Among populations, the absolute risk of CHD at a given BP varies substantially. If the absolute risk of CHD is taken as a criterion for the use of antihypertensive therapy, this finding will have major implications for clinical practice in different parts of the world.

NEJM January 6, 2000; 342: 1-8 Original investigation by the "Seven Countries Study Research Group", first author Peggy C W van den Hoogen, National Institute of Public Health and the Environment, Bilthoven, the Netherlands.

Comment:

We may be moving away from the term "hypertension" What is hypertension for you may not be hypertension for me. The word implies yes or no — either you have it, or do not have it, depending on an arbitrarily set mean BP level. The study demonstrates that this may be very misleading. Risk of CHD is multifactorial. All factors must be taken into account and efforts made to influence *all of them* as much as possible. An individual with a BP of 140/80 who has no other risk factors may be reassured. For another individual with the same BP who has a high BMI, lipid abnormalities, and smokes we should intervene with all 4 factors including therapy to lower BP.

There has been a continuing debate — is "hypertension" a valid clinical diagnosis?

A. Some have contended that there is a distinct cut-point. Those above it are at risk; those below are not at risk.

B. Some have contended that there is no cut-point; risk rises with each increase in BP.

I believe Bs are carrying the day. RTJ

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1-2 BLOOD PRESSURE AND THE RISK OF CARDIOVASCULAR DISEASE.

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

"There are several important reasons to question the appropriateness of continuing to focus primarily on hypertension and its treatment, as opposed to the broader concept of blood-pressure-related disease and its prevention."

The preceding study reported, over a 25-year period, the relative risk of death from CHD rose continuously with increasing levels of systolic and diastolic BP. There was no abrupt increase in risk at levels of BP typically used as

criteria for hypertension. “There was no clearly defined lower level of BP below which the risk did not continue to decline.”

Indeed, the associations between BP and risk of death from CHD imply that any given difference in BP between persons is associated with an approximately constant difference in the relative risk of death due to CHD, irrespective of whether the BP is high enough to be termed “hypertension”. (*Ie, in populations, the risk of death from CHD rises with each 10 mm increase in systolic BP — persons with systolic of 130 are more at risk than those with a systolic of 120; and at less risk than those with a systolic of 140, and so on.)*

Indeed, since there are many more persons with “normotension”, than with “hypertension”, perhaps paradoxically, the total burden of BP-related disease is greater in the group with “normotension”.

The absolute risk of CHD death was highest in the group with BP ≥160/95. But in different populations, the risk of death among those with this BP varied by a factor of 3 to 4.

Prognosis among persons with “hypertension” is highly variable, depending on factors other than BP — sex, age, other risk factors, target organ damage, and history of cardiovascular disease.

“The usefulness of hypertension as an independent diagnostic category appears to be limited, and it is arguable from both a public health and clinical perspective, that we should refocus our efforts toward the lowering of blood pressure and the prevention of blood-pressure-related diseases, in both hypertensive and *nonhypertensive* persons. (Ie, in some individuals lowering BP from 140/85 to 125/80 may be more beneficial than lowering BP from 170/95 to 140/90.

“There is clearly a strong rationale for expecting many patients who are at high risk for major cardiovascular events (whether they are ‘hypertensive’ or not) to benefit from a substantive reduction in blood pressure.” “Even for high risk patients who are already being treated with a beta-blocker or an angiotensin-converting-enzyme inhibitor, there may well be additional benefits of further reductions in blood pressure beyond those typically produced by either of these drugs alone.”

NEJM January 6,2000; 342: 50-52 Editorial by Stephen MacMahon, University of Sydney, Australia.

Comment:

Treat the person, not the BP.

This begs the question — how far should BP be lowered? I believe this is a decision to be made for each individual. It depends largely on any adverse effects which may accompany the therapy. RTJ

1- 3 EFFECTS OF AN ANGIOTENSIN-CONVERTING-ENZYME INHIBITOR, RAMIPRIL, ON CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

The usual major risk factors for cardiovascular disease do not fully account for the risk. Activation of the renin-angiotensin-aldosterone system may have an important role in increasing risk. A recent meta-analysis of secondary prevention in over 9000 patients reported that treatment with ACE-inhibitors reduced risk of myocardial infarction by 23%. This was independent of ejection fraction, the cause of the heart disease, concomitant use of medications, diabetes, and/or blood pressure.

This suggests that ACE inhibitors may have a role in preventing myocardial infarction in a broad range of patients, not just those with a low ejection fraction. ACE inhibitors may also reduce the risk of stroke and complications of diabetes.

This study assessed the role of the ACE inhibitor ramipril (*Altace*, a long-acting ACE inhibitor) in high risk patients who did not have left ventricular dysfunction or heart failure.

Conclusion: Ramipril was associated with reduced rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who were not known to have low ejection fractions.

STUDY

1. Entered over 9000 high-risk patients (all over age 55; mean = 66). All had evidence of vascular disease or diabetes *plus* one or more other cardiovascular risk factors (history of myocardial infarction, stable angina, unstable angina, stroke, peripheral vascular disease, elevated total cholesterol, low HDL-cholesterol, or current cigarette smoking). [*This was essentially a secondary prevention trial. RTJ*]
2. None had known heart failure or low ejection fraction.
3. Most were taking other medications (beta-blocker, aspirin, lipid-lowering agents, diuretics, calcium blockers). These were continued.
4. Randomized to: 1) ramipril 10 mg daily, or 2) placebo.
5. Primary end point = composite of myocardial infarction, stroke, or death from cardiovascular disease.
6. Follow-up = 5 years.

RESULTS

1. Study was terminated early at 4.5 years because of favorable outcomes.
2. Fourteen percent of ramipril patients reached the primary end point vs 17.5% of the placebo patients.
   NNT(benefit 1 patient over 4.5 years)= 28
3. Individual outcomes:

	Ramipril (%)	Placebo (%)	Difference (%)
Death from cardiovascular disease	6.1	8.1	2
Myocardial infarction	9.9	12.3	2.4
Stroke	3.4	4.9	1.5
Death from any cause	10.4	12.2	1.8
Revascularization procedures	16	18.3	2.3
Cardiac arrest	0.8	1.3	0.5
Heart failure	9	11.5	2.5

   (*The number needed to treat for 4.5 years for each outcome to benefit one patient would range from 200 to 40. RTJ*)
4. Benefit began within 1 year and persisted throughout.
5. Ramipril was well tolerated. Equal numbers of patients in each group withdrew (33% in each).

Seven % of ramipril group withdrew because of cough.

DISCUSSION

1. Ramipril was beneficial in a broad range of patients at high risk of cardiovascular disease who did not have evidence of systolic dysfunction or heart failure.
2. The spectrum of patients who benefited was quite broad. Ramipril was effective in all subgroups. This complements results of previous studies of patients with low ejection fractions, heart failure, or acute myocardial infarction.
3. The magnitude of benefit with respect to the primary outcome was at least as large as that of other secondary prevention measures (beta-blockers, aspirin, and lipid lowering agents). The benefits were in addition to other drugs.
4. Only a small part of the benefit could be attributed to a reduction in BP. (The majority did not have hypertension. BP declined by only 3/2 mg Hg in the ramipril group vs the placebo group.
5. "Angiotensin-converting-enzyme inhibitors will be beneficial for patients who are at high risk for heart failure, irrespective of the degree of left ventricular systolic dysfunction."
6. Treating 1000 patients for 4 years will prevent about 150 events in approximately 70 patients. [NNT(prevent 1 event over 4.5 years) = 7. NNT (prevent any event in one patient over 4 years) = 15]

   (*This assumes that every one of the 1000 will continue the drug without interruption for 4 years. If the outcome is based on "intention to treat" results will be less favorable. RTJ*)

CONCLUSION

The ACE inhibitor ramipril reduced rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who were not known to have a low ejection fraction or heart failure.

NEJM January 20, 2000;342: 145-53 Original multicenter investigation by The Heart Outcomes Prevention Evaluation (HOPE) Study Investigators.

Comment:

Note that 1 in 3 did not complete the study. In primary care practice, fewer still will complete 4 years of treatment uninterrupted. RTJ

1-4 ACE INHIBITION IN CARDIOVASCULAR DISEASE

(This editorial makes some additional comments.)

The renin-angiotensin-aldosterone system likely evolved millions of years ago as an adaptive mechanism to protect circulatory integrity, intravascular volume, and perfusion pressure of vital organs. For many years the emphasis was on the endocrine functions of the system, including salt and water retention, vasoconstriction, release of aldosterone, and thirst. The system was thought to be activated in response to a decrease in intravascular volume or inadequate perfusion as a way of maintaining adequate blood flow. It is now known that the system operates in concert with an even more fundamentally complex tissue-based molecular signaling

pathway involving angiotensin II. This simple peptide has a more primitive biologic role than restoring circulatory integrity. It most likely provides an adaptive or reparative response to tissue injury.

Some of the features of the repair process subserved by angiotensin II and aldosterone have ultimately proved to be maladaptive in the long-term. They contribute to increased systemic vascular resistance, circulatory congestion, myocardial fibrosis and hypertrophy, endothelial dysfunction, rupture of plaques, and reduced fibrinolysis. "There is a price to pay for the short-term benefits of the renin-angiotensin-aldosterone system."

Hypertension and heart failure have been major therapeutic targets for ACE inhibitors, but by the 1980s it was clear that these agents were doing something beyond simply reducing systemic vascular resistance.

"It is reasonable to prescribe ramipril for patients who are similar to those enrolled in the HOPE study – high-risk patients with a history of coronary disease, peripheral vascular disease, stroke, or diabetes mellitus and at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol levels, cigarette smoking, or documented microalbuminuria." This will greatly broaden the spectrum of patients who can be treated effectively.

NEJM January 20, 2000;342:201-02 Editorial by Gary S Francis, Cleveland Clinic, Cleveland, Ohio

Comment: This sea change in understanding the physiology of the renin-angiotensin-aldosterone system will open the door to new pharmacological interventions in clinical practice. One important question is — is it worth it? RTJ

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1-5 EFFECT OF RAMIPRIL ON CARDIOVASCULAR AND MICROVASCULAR OUTCOMES IN PEOPLE WITH DIABETES MELLIUS: Results of the HOPE Study and MICRO-HOPE Study

People with diabetes experience a 2 to 5 times higher risk of cardiovascular mortality than those without diabetes. About 1 in 20 middle-aged and elderly persons with type 2 diabetes experiences a cardiovascular event (including death) each year.

The presence of other risk factors increases risk.

Other studies suggest that angiotensin-converting enzyme inhibitors (**ACE)** delay or prevent cardiovascular outcomes. Benefit has been demonstrated after myocardial infarction, in the presence of hypertension, and in patients with low ejection fraction and heart failure. ACE inhibitors may also prevent overt nephropathy and other microvascular outcomes in patients with diabetes.

This study assessed whether the ACE inhibitor ramipril (*Altace*) can lower risks of cardiovascular events in patients with diabetes.

Conclusion: Ramipril reduced cardiovascular events and overt nephropathy.

STUDY

1. Entered over 3500 patients with diabetes. All were over age 55 (mean = 65); all but 2% with type 2 diabetes. Mean BP = 140/80.

2. All had a previous cardiovascular event (coronary artery disease, stroke, peripheral artery disease), *or* at least one other cardiovascular risk factor (total cholesterol over 200 mg/dL, HDL cholesterol under 35 mg/dL, hypertension, microalbuminuria [30 to 300 mg/d], or current smoking.*)*

   (This was a study of high-risk individuals — ie, individuals with both diabetes and established cardiovascular disease. And also of individuals with diabetes who might be considered at higher risk because of additional risk factors. Few will have a low total cholesterol and a high HDL-cholesterol. Many will have hypertension, microalbuminuria, and be smokers. Few would be excluded.)

3. None had overt nephropathy (albuminuria > 300 mg/d), heart failure, or low ejection fraction.
4. Randomized to 1) ramipril 10 mg daily [titrated up from 2.5 mg] or 2) placebo.
5. The majority was taking other drugs (aspirin, diuretics, beta-blockers, calcium blockers, hypolipidemic drugs, singly or in combination). These were continued.
6. Follow-up = 4.5 years

RESULTS

1. Ramipril was associated with a lower risk of myocardial infarction by 22%; stroke by 33%; cardiovascular death by 37%; total mortality by 24%; and overt nephropathy by 24%.

   (*By my calculation, absolute reductions of 1.9% to 4.5% over 4.5 years in each of these outcomes – NNT(benefit-4.5 years) = 20 to 50. RTJ)*
2. After adjustment for changes in BP subsequent to ramipril therapy (-2.4 / -1.0 mg Hg) the combined primary outcome (myocardial infarction, stroke, or cardiovascular death) was reduced by 25%
3. About 1/3 of subjects in both groups did not complete the study. Cough caused 7% of the ramipril group to stop.

DISCUSSION

1. The study was stopped 6 months early because of consistent benefit.
2. "Benefit was apparent irrespective of whether participants had a history of cardiovascular events, hypertension, or microalbuminuria, were taking insulin or other antihyperglycemic agents, or had type 1 or type 2 diabetes."
3. Ramipril was also associated with a lower risk of renal failure and laser therapy for retinopathy.
4. Ramipril had no long-term effect on glycemic control.
5. "When the major cardiovascular and microvascular events are taken into account, 15 high-risk people with diabetes would have to be treated with ramipril for a median of 4.5 years to prevent one individual from having a myocardial infarction, stroke, cardiovascular death, admission to hospital for heart failure, a revascularization procedure, development of overt nephropathy, laser therapy for retinopathy, or renal dialysis."

   NNT (benefit one patient over 4.5 years) = 15
6. These benefits are much greater than can be attributed to any effect on BP.
7. ACE inhibitors may have a protective effect on the arterial wall. Angiotensin II is a powerful direct

vasoconstrictor and promotes vascular smooth muscle growth. It may also promote plaque rupture. Bradykinin, the level of which is increased by ACE inhibition, is a direct vasodilator. The effect of ACE inhibitors may be mediated by lowering of angiotensin II and increasing bradykinin concentrations.

8. "ACE inhibition with ramipril is most appropriately viewed for this study as a preventive intervention with multiple mechanisms of benefit, including lowering of blood pressure."

CONCLUSION

Ramipril was beneficial in reducing cardiovascular events and overt nephropathy in persons with diabetes. Benefit was greater than that attributable to decrease in BP. This treatment represents a vasculoprotective and renoprotective effect.

Lancet January 22, 2000; 355: 253-59 Original multicenter investigation by the Heart Outcomes Prevention Evaluation (HOPE) Study Investigators.

Comment:

This study presents a widespread application for ACE inhibition. Almost all older patients with diabetes will have at least one additional risk factor.

Altace 10 mg daily would cost wholesale over $1400 a year. Ask the patient — Would a 1 in 15 chance of preventing a cardiovascular event (while incurring possible adverse effects) over 5 years be worth $7000 to you?

For preventive drug regimens such as this, patients must understand that intermittent therapy or discontinuation will negate any benefit. Choosing to accept this therapy or not is a personal decision.

Not all patients at baseline have the same absolute risk of a future event. Effectiveness of treatment can be increased by choosing higher-risk individuals for treatment. (Ie, those with more risk factors.) Clinicians can make a reasonable estimate of risk . RTJ

1-6 HOPE AND EXTENSION OF THE INDICATIONS FOR ACE INHIBITORS?

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

"The trial was stopped early according to predefined rules because of an overwhelming effect of ramipril on the primary endpoint, a 22% reduction in a composite measure of myocardial infarction, stroke, and death from cardiovascular causes." Significance was also achieved on outcomes as diverse as myocardial infarction, revascularization, heart failure, cardiac arrest, and worsening angina.

These findings have considerable implications for clinical practice. They indicate that virtually *all* patients with a history of cardiovascular disease, not just those with an acute myocardial infarction or heart failure, may benefit from ACE inhibition.

Current US guidelines for treatment of hypertension recommend diuretics or beta-blockers as first line therapy, reserving ACE inhibitors for more serious cases of heart disease. Patients in the study were on maximum therapy for major risk factors, including hypertension. The observed benefit of ramipril was *in addition* to the

drugs many subjects were already taking (beta-blockers, calcium blockers, diuretics, aspirin, and lipid-controlling agents). Should ACE inhibitors then be added to these patients? The study cannot provide an unequivocal answer to this question. The stricter JNC VI guidelines for a target BP of 130/ 85 would increase the numbers of patients who receive drug therapy. Guidelines already include ACE inhibitors as one of the first-line agents.

Lancet January 22, 2000; 355: 246-47 Editorial by Nish Chaturvedi, University College, London

Comment:

What are the clinical implications of the HOPE study? I believe, as a result, ACE inhibitors will be used more frequently and earlier — not for their BP-lowering effect, but for their vascular and renal-protective effects.

Many older patients with diabetes (I believe most) have at least one other risk factor which would place them in the high-risk group eligible for ACE therapy. The NNT for 4.5 years with ACE therapy to prevent any one of the adverse outcomes (although which one would be undetermined) is relatively low. In addition, ACE inhibition in patients with diabetes protects against renal deterioration.

For high-risk patients without diabetes, the authors state that treating 100 such patients for 4 years will prevent 15 events in about 7 patients.

I believe primary care clinicians should now point out to high-risk patients, including many with diabetes, the benefit/harm-cost of ACE inhibitors. Clinicians should inform patients about, not only the benefits as we now judge them, but also the harm (ramipril was well tolerated, cough the most prevalent adverse effect) and the cost, which is high.

In addition, it must be made clear at the onset that this therapy requires a long-term commitment. (Note that about one of every 3 to 4 patients in the studies withdrew. Withdrawals will be more frequent in primary care clinical practice. Short-term is a waste of money and exposes patients needlessly to possible adverse effects. RTJ

1-7 VITAMIN E SUPPLEMENTATION AND CARDIOVASCULAR EVENTS IN HIGH-RISK PATIENTS

Experimental studies report that oxidative modification of low-density lipoprotein is an important step in the development and progression of atherosclerosis. An inverse relation has been observed between coronary heart disease (**CHD**) and consumption of fruits, vegetables and other foods containing vitamins, especially vitamin E. But, observational studies cannot distinguish whether the lower risk is associated with the vitamin E content or with other lifestyle or dietary factors. Results of randomized, controlled studies of the relation between CHD and vitamin E have been conflicting.

This study, a companion to the preceding trial, evaluated the association between a high dose of vitamin E and incidence of CHD.

The subjects were the same as in the preceding trial – over 9000 persons at high risk of CHD. Half were randomized to vitamin E (400 IU per day) from high bioavailability natural sources; half to placebo

At 4.5 years, there was no difference between groups; 16.2% assigned to vitamin E and 15.5% assigned to placebo had the primary outcome of a composite of myocardial infarction, stroke, and death from cardiovascular disease. There were no significant differences in any individual cardiovascular outcome or in death from any cause.

Conclusion: Vitamin E, in this cohort of high-risk patients, had no apparent benefit on cardiovascular outcomes. It is very unlikely that vitamin E given for 5 years has any clinically worthwhile effect on cardiovascular disease.

NEJM January 20,2000;342: 154-60 Original multicenter investigation by the Heart Outcomes Prevention Evaluation Study (HOPE) investigators

The authors comment that the large Physician's Health Study (which demonstrated the benefit of low-dose aspirin in primary prevention of myocardial infarction) did not find any benefit from beta carotene (another antioxidant of different action) after 12 years.

Comment: What is the clinical message of a negative study? I believe primary care clinicians can now definitely consider the benefit/harm-cost of vitamin E, at least for cardiovascular disease prevention, to be a negative. Benefit is nil, and, although the harm is also nil, the cost over several years can be significant and is worthless.

The US Institute of Medicine recently issued a report on Dietary Reference Intakes stating that insufficient evidence exists to support claims that megadoses of vitamins C and E, carotenoids, or other antioxidants can prevent chronic disease. *Lancet* April 22, 2000; 1433 "News" form the *Lancet* staff.

This does not preclude further studies concerning possible benefits of vitamin E – as in cancer prevention. However, the antioxidant theory, at least as applied to clinical medicine, seems to be rapidly running out of steam. One wonders how it became enthusiastically embraced so quickly. . RTJ

1-8 PENICILLIN FOR ACUTE SORE THROAT: Randomised Double Blind Trial of Seven Days Versus Three Days Treatment or Placebo in Adults.

In patients with sore throat due to group A beta-hemolytic streptococci, penicillin accelerates resolution of symptoms and reduces the number of suppurative complications.

Penicillin is considered superior to alternatives because of fewer adverse effects and lower costs, and because group A Beta-hemolytic streptococci have not developed resistance.

Prevention of rheumatic fever is no longer the main reason to treat patients with penicillin in western Europe because of the low incidence of this complication.

Traditionally, a regimen of 10 days has been advocated to maximize eradication of the bacteria. Shorter courses usually resolve symptoms. The Netherlands national guidelines recommend 7 days of penicillin, although empirical evidence for this recommendation is lacking.

This study asked: Is a 3-day equally effective to a 7-day treatment in resolving symptoms of streptococcic pharyngitis?

Conclusion: A seven day course was superior for resolution of symptoms. The 3 day course was not much more effective than placebo.

STUDY

1. Randomized, double-blind, placebo-controlled, multicenter trial entered over 550 patients with acute sore throat.
2. All had at least 3 of 4 criteria leading the clinicians to suspect group A beta-hemolytic infection: 1) fever, 2) absence of cough, 3) swollen tender anterior cervical lymph nodes, and 4) tonsillar exudate. (These criteria make group A beta-hemolytic streptococcal infection more likely. Most sore throats are viral infections and do not require antibiotic therapy.)
3. About half of all patients had cultures positive for group A streptococci. About a third had non-group A streptococci.
4. Randomized to: 1) penicillin V 250 mg 3-times daily for 7 days, 2) penicillin V 250 mg 3-times daily for 3 days, and 3) placebo.
5. Primary outcome was the duration of symptoms defined as the number of days until permanent resolution of either pain or impaired daily activities took place.

RESULTS

1. Eradication of group A streptococcus: 7-day course — 72%; 3-day course — 41%, placebo — 7%
2. The duration of symptoms was defined as the total number of days until *permanent* resolution of either pain or impaired daily activities occurred. (Eg, if the patient was symptom free at day 3 but developed symptoms again at days 4 and 5 which resolved at day 6 or 7, the duration was calculated as 4 or 5 days.)
3. The 7-day patients showed a *permanent* resolution of sore throat 1.9 days sooner than the 3-day group, and 1.7 days sooner than the placebo group. Although most patients in the 3-day group had resolution of symptoms at day 3, 40% had a recurrence of symptoms in days 4 to 7. The 7-day patients resumed their daily activities a total of 2 days earlier than those in the 3-day group or in the placebo group.
4. Indeed, the 3-day group did not have a permanent resolution of symptoms sooner than the placebo group.
5. Analgesic use declined more rapidly in the 7-day group from day 4 through day 7.
6. Seven-day penicillin was also effective in relieving symptoms in patients with non-group A streptococci.
7. Six patients in the placebo group had streptococcal complications: peritonsillar abscess, erysipelas, impetigo, and transient polyarthritis.

DISCUSSION

1. Penicillin treatment for 7 days shortened the duration of both sore throat and impairment of daily activities by about 2 days as compared with 3-day treatment or with placebo.
2. Benefit occurred also in patients with non-group A streptococci.
3. The selection of patients for therapy was based on clinical features, not on results of the rapid detection tests

for the group A antigen. In the Netherlands, treatment in primary care is founded on clinical grounds, not on bacteriological grounds.

4. Although complications of streptococcal infections occurred more often in the placebo group (*see above*), recurrences of symptoms were more common during the week in the 3-day group than in the placebo group. The 3-day group also had more recurrences in the following 6 months. This may have been because the short course reduced the natural immune response and suppressed the streptococci without eradicating them. The risk of recurrence over the following 6 months was similar in the placebo and the 7-day treatments.

CONCLUSION

A seven day course of penicillin was effective in reducing duration of symptoms and reducing risk of suppurative complications. It is also effective in non-group A infections and reduced the risk of recurrent sore throat over the next 6 months.

A 3-day course was not any more effective than placebo in reducing total days of symptoms.

BMJ January 15, 2000;320: 15-154 Original investigation, first author Sjoerd Zwart, University Medical Center, Utrect, Netherlands.

Comment:

The 3-day course did seem to protect against complications of streptococcal pharyngitis, but was not effective (as compared with placebo) in reducing the duration of symptoms.

The old recommendation was to be sure the patient continued penicillin for a full 10 days. This was directed mainly because of the risk of rheumatic fever. Since rheumatic fever is now less common in the US, I believe a 7-day course should be recommended if the decision is made to use antibiotic therapy RTJ

1-9 SORE THROATS AND ANTIBIOTICS

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

"The liberal use of antibiotics for sore throat is increasingly frowned on."

There are 3 reasons why a clinician might use antibiotics for sore throat: 1) to reduce risk of complications, 2) to shorten duration, or reduce the severity of symptoms, and 3) because of factors related to the consultation (perceived patient demand; ways of terminating the consultation).

Great variation in practice persists despite guidelines from evidence-based sources. "General practitioners do not access evidence-based information well."

What does the evidence show? 'Antibiotics reduce the incidence of both suppurative (quinsy) and non-suppurative complications of sore throat. They reduce the duration of symptoms. (*The preceding study reports this occurs only if the antibiotic is continued for 7 days.*) However, the benefit is so modest that one can dispute its clinical importance. This is because the size of the effect is small (however statistically significant) or because

the chance of suffering complications is so tiny that even a reasonable relative reduction conferred by antibiotics yields a similarly unimportant absolute benefit.

"There is no single course of action that will suit all, or even most, patients." The evidence must be applied in different ways according to local conditions. These will include environmental factors (places in the world where acute rheumatic fever is common), history (previous middle ear infection), and social factors. "General practitioners put as much weight on social factors as on the physical examination in deciding whether or not to use antibiotics. Both patients and their doctors dance delicately around the complicated negotiation of antibiotics for upper respiratory infections, each aware of the other's sensibilities."

"At some point the benefits and harms resulting from treatments, . . . including emerging antibiotic resistance and costs to society, are so finely balanced that patients and their doctors must decide on a choice that is likely to be tipped one way by personal preference alone."

"To expect a one line answer from the evidence (a guideline, for example) is to ask too much."

BMJ January 15,2000; 320: 130-31 Editorial by Chris Del Mar, University of Queensland, Brisbane, Australia.
Comment:

All primary care clinicians are aware of the growing resistance to antibiotics. They do pause when prescribing an antibiotic. One still valid way of reducing use is to inform the patient that it is likely that the symptoms (of bronchitis, sinusitis and sore throat) will improve with simple symptomatic management, and give an insistent patient an "if" prescription to be filled after 2 or 3 days if the symptoms are not improved. (The majority will be improved, and many prescriptions will not be filled.)

A great gulf separates the results of "evidence-based" medicine from its application to individual patients – a gulf, for want of a better term, called the "art" of medicine. As the editorialist suggests, application depends on much more than the "number needed to treat". A favorable NNT (to obtain benefit from a therapy for one patient) is 10. What about the other 9? When consulting with an individual patient, clinicians and the patient herself often decide that she is likely to be the one, and ignore the higher possibility that she may be among the 9, thus being exposed needlessly to a potentially harmful and costly drug. RTJ

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1-10 MENOPAUSAL ESTROGEN AND ESTROGEN-PROGESTIN REPLACEMENT THERAPY AND BREAST CANCER RISK

No doubt hormone replacement therapy (**HRT**) increases risk of breast cancer (**BC**). In 1997 a collaborative study[1] of over 90% of the world's epidemiological data reported that longer duration of recent (not over 5 years past) use increases risk. The risk was higher in lean women. The study also reported that BCs associated with HRT were less clinically advanced.

The data were insufficient to determine whether combined estrogen-progestin increases risk beyond that of estrogen alone.

This study was designed to determine if the risk is greater with combined estrogen-progestin.

Conclusion: It is.

STUDY

1. A nation-wide cohort study of breast cancer screening followed over 46 000 postmenopausal women (mean age 58 years at baseline).
2. Determined incident BC by recency, duration, and type of hormone use in 22 years of follow-up.

RESULTS

1. Identified 2082 incident cases of BC.
2. Increases in risk were restricted to use within the previous 4 years. (Ie, women who stopped either regimen over 4 years earlier experienced no increase in risk.)
3. Compared with non-users, the relative risk (RR) of BC in estrogen-alone users was 1.2; and 1.4 for estrogen-progestin users.
4. RR increased for each year of use (within the past 4 years) by 0.01 for estrogen-alone, and 0.08 for estrogen-progestin users.
5. Among women with a BMI less than 24.4 kg/m^2 RR increased with each year of use of estrogen alone by 0.03, and for estrogen-progestin by 0.12. (*Ie, duration of use for past 4 years only. Other studies report that discontinuation for 5 years eliminated risk. RTJ*)
6. Risk did *not* increase in *heavier women* with either regimen.

DISCUSSION

1. "Our results suggest that combined estrogen-progestin regimen is associated with greater increases in breast cancer risk than estrogen alone."
2. No increased risk from either regimen occurred in women with a BMI over 24.4.
3. "It is important to consider the type of hormone regimen as well as individual characteristics of the woman, such as body mass index."

CONCLUSON

Hormone replacement therapy with estrogen-progestin increased risk of breast cancer beyond that of estrogen alone.

JAMA January 26, 2000; 283; 485-491 Original investigation by the Breast Cancer Detection Demonstration Project, first author Catherine Schairer, National Cancer Institute, Bethesda, MD

1 *Lancet* 1997;350:1047-59

Comment:

What is the clinical application of this data? Many women resist HRT because of a fear of BC. This study may provide some reassurance: 1) If HRT is discontinued over 4 years prior, any increased risk of BC was no longer evident. 2) Heavier women need worry less.

Should women with an intact uterus who are taking combined therapy switch to estrogen-alone? Certainly not. The added protection against endometrial cancer in women with a uterus must overweigh any increase in risk of BC

Should women stop taking HRT because of the increased risk of BC? I believe this personal decision depends on individual risk of BC (family history, prior BC, fear of cancer) after being completely informed of risks and benefits.

As with most studies the investigators stress relative risks. Absolute risks are more meaningful. By my calculations from their table 1 p 488:

	No. of person-years	No. of cases of BC	No./1000 person-years	Excess BC/1000 person-years
No ever-use	196 000	761	3.8	-
Estrogen-alone	179 401	805	4.4	0.6
Estrogen-progestin	17 428	101	5.7	1.9

Note that BC was common in never-using women . The additional risk associated with HRT was less than the basic risk in non-users. However, I believe, if BC develops, clinicians and patients alike would likely blame the HRT.

Women who take HRT of either type should be followed more closely with clinical exam and mammography. RTJ

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1-11 POSTMENOPAUSAL ESTROGENS – OPPPOSED, UNOPPOSED, OR NONE OF THE ABOVE

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

Cyclical use of progestin increases mitotic activity in the breast. Studies now provide firm evidence that addition of progestin to estrogen does *not* reduce the risk of BC (as some have hypothesized), but suggests that the risk is actually increased.

The editorialists suggest the following reasonable considerations:

1) The risks of HRT-associated BC are determined by duration of use. Short-term use (eg, 2 to 3 years) for relief of menopausal symptoms should not be influenced by fear of BC.
2) The first issue is whether HRT is needed at all. Does reducing risk of fractures and coronary heart disease justify use? “Reducing risk of fractures and coronary heart disease rarely will provide sufficient justification because avoidance of smoking, performance of regular exercise, and consuming a good diet are effective preventive measures.” A variety of alternative pharmacological means of prevention are available, including statins, bisphosphonates. and selective estrogen

modulators (SERMs; raloxifene; tamoxifene). The aim of SERMs is to prevent osteoporosis without stimulating the endometrium while reducing BC risk. The long-term consequences of SERMs, however remains unknown.

"The commonly held belief that aging routinely requires pharmacological management has unfortunately led to neglect of diet and lifestyle as the primary means to achieve healthy aging."

JAMA January 26, 2000; 283: 534-35 Editorial, first author Walter C Willett, Harvard School of Public Health, Boston, Mass.

Comment:

Postmenopausal concerns include: menopausal symptoms, osteoporosis, and atherosclerotic vascular disease. The goal of therapy is to reduce risk with the fewest adverse effects. As the editorialists state, lifestyle measures are basic. I believe, however, that most women require additional (pharmacological) therapy to control symptoms and reduce risk.

Menopausal symptoms: There is no substitute for HRT to control troublesome menopausal symptoms. I doubt the most consistently healthy lifestyle will prevent menopausal symptoms. Use for several years is safe. After menopausal symptoms wane, women may wish to switch to another drug to delay osteoporosis and possibly reduce risk of cardiovascular disease.

Osteoporosis prevention: Women have several choices: healthy lifestyle; continued HRT; bisphosphonate (eg, alendronate); and SERMs.

Healthy lifestyle. I believe osteoporosis will progress despite the most healthy lifestyle. I believe pharmacological intervention will be needed to retard development of osteoporosis. As usual, taking a pill will be much easier than following a dedicated healthy lifestyle. Which one to use? No reason not to use both.

HRT is among the most effective drug applications in preventing loss of bone mass. Women who are informed about risks (eg, breast cancer) and are not at increased risk of BC may wish to continue into older age. Some may wish to take a different drug after menopausal symptoms have waned, depending on their acceptance of risk of BC.

Alendronate is effective in delaying and treating osteoporosis. The benefit/harm-cost ratio may be high despite a wholesale cost (of *Fosamax*) exceeding $8000 for 10 years. Used properly, the drug is well tolerated.

SERMs have the additional benefit of reducing risk of breast and endometrial cancer. They are effective in reducing bone loss. They do not control menopausal symptoms, indeed may increase hot flashes. Wholesale cost of *Evista* 10 mg daily over 10 years will exceed $8000.

Cardiovascular disease prevention: At the present state of knowledge, I believe HRT will likely *increase* the risk of coronary heart disease during the first year or two of its application, particularly when started in older women with other risk factors. Thereafter it may or may not be protective. The enthusiasm

regarding estrogen as a protective agent against coronary disease has been dampened by consideration of the "healthy user" effect. And as noted, by the increased risk of breast cancer. Statin drugs given to patients at high risk will be more beneficial in reducing risk than HRT.

I do not see any contraindication to added low-dose aspirin in most postmenopausal women. RTJ

1-12 RISK ASSESSMENT OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN PRIMARY CARE: Cross Sectional Study Evaluating A Range of Diagnostic Tests

Identification and treatment of patients with left ventricular systolic dysfunction (**LVSD**) improves survival and reduces morbidity. About 3% of the adult population has systolic dysfunction. Half of these are asymptomatic and can be identified only by objective methods, usually echocardiography.

How should we identify individual patients with dysfunction to refer for echo? Those with history of ischemic heart disease are an obvious risk group, but greater sensitivity is achieved by examining patients with signs suggestive of heart disease.

This study examined how primary care MDs might identify patients at increased risk of LVSD in order to decide on referral for echo.

Conclusion: Three simple clinical variables identified patients at higher risk for LVSD.

STUDY

1. Cross sectional survey screened over 2000 patients age over 40 by questionnaires and case records. Identified 357(16%) with past or present signs or symptoms of heart disease.
2. Of these, 126 were eligible for the study and consented to examination. All had characteristics which made them suspect of a high likelihood of systolic dysfunction: documented heart disease, past or present history suggestive of heart disease, current treatment for hypertension, smoking, and others. (*See table 1 p 221*). These patients are easily identified in primary care practice.
3. All subsequently underwent echocardiography. Defined systolic dysfunction as an ejection fraction less the 45%.
4. Determined clinical variables related to low ejection fractions.

RESULTS

1. Fifteen patients of the 126 (12%) had left ventricular dysfunction determined by echo.
2. Three clinical variables were significantly related to left ventricular dysfunction:
   1) ECG with Q waves, left bundle branch block, or ST-T segment changes, 2) resting pulse rate greater than simultaneous diastolic BP, and 3) elevated plasma atrial natriuretic peptide.

3. Only one of 60 patients with a normal ECG had systolic dysfunction regardless of the presence of the other 2 variables. "A normal electrocardiogram was the only clinically useful test to rule out systolic dysfunction with a sufficiently high accuracy."
4. Risk was higher in patients with an abnormal ECG and one or two of the other variables. Those with all 3 variables may be treated as if they have systolic dysfunction ". . .since they most certainly have it".
5. A single measurement of natriuretic peptide does not discriminate between minor degrees of systolic dysfunction and preserved systolic function. However, it may be useful to indicate which patients require further clinical assessment.
6. This algorithm, however, could *not* identify everyone with systolic dysfunction in the community.

CONCLUSION:

A normal electrocardiogram implies a low risk of left ventricular systolic dysfunction. An abnormal ECG combined with either a high atrial natriuretic peptide or a resting heart rate greater than diastolic BP, or both, identified patients with left ventricular systolic dysfunction.

BMJ January 22, 2000;320:220-24 Original investigation, first author Olav Wendelboe Nielsen, Copenhagen University Hospital, Denmark.

Comment:

This study measured *atrial* natriuretic peptide (the peptide produced by the atria when stretched in heart failure. "Brain" natriuretic peptide (*despite the misleading connotation*), is produced by the stretched ventricles and may be a more sensitive measure of ventricular dysfunction. But, as noted, by itself it is not a good indicator of left ventricular dysfunction.

The important clinical message, which has been noted by others, is that a normal ECG will almost always rule *out* left ventricular systolic dysfunction. Obviously an abnormal ECG cannot rule *in* dysfunction. RTJ

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1-13 EFFECTS OF INFLUENZA VACCINATION OF HEALTH-CARE WORKERS ON MORTALITY OF ELDERLY PEOPLE IN LONG-TERM CARE

Grouping frail elderly people in long-term care creates an environment that is likely to allow rapid spread of influenza. Case-control studies report that vaccination of this group of individuals is associated with a decreased risk of pneumonia and death. However, protection afforded by vaccination of the frail elderly is frequently incomplete, in part because of their inability to develop adequate protective antibodies.

Vaccination of health-care workers (**HCW**) in long-term care facilities may be an additional measure protecting the elderly residents. A previous study reported that about 1 of every 4 hospital staff in winter had evidence of influenza infection demonstrated by serological evidence. The potential is high for flu to be brought into elder-care homes.

This study assessed the effect of flu vaccination of HCW on incidence of death among the elderly in long-term facilities.

Conclusion: Vaccination of the health-care workers was associated with a decline in mortality among the elderly in-patients.

STUDY

1. In a parallel group study, health-care workers in 20 long-term elder-care hospitals (in 12 sites with a total of over 1400 elderly patients) were randomly offered, or not offered, flu vaccine.
2. Recorded deaths of the elderly patients over a 6-month winter period.

RESULTS

1. About 50% of health-care workers offered the vaccine accepted. Only 5% of those for whom vaccine was *not* offered received vaccine. However, more elderly patients in the vaccine-offered-to-health-care-workers hospitals received vaccine (48% vs 33%). This may have confounded results somewhat. But, there was no clear association between vaccination uptake among the elderly patients with mortality.
2. Mortality was 13.6% in the vaccine hospitals vs 22.4% in the no-vaccine hospitals.
3. About 6% of each group of elderly were PCA-positive for influenza virus. (Ie, vaccination did not prevent infection.)

DISCUSSION

1. Vaccinating health-care workers was associated with a decrease in mortality of elderly hospitalized patients.
2. "There is good evidence therefore, that a program of vaccination of health-care workers substantially lowers mortality among elderly patients in long-term care, probably through prevention of nosocomial transmission."
3. Many UK geriatricians believe that routine influenza vaccination of the frail elderly is unlikely to be beneficial.

CONCLUSION

Vaccination of health-care workers was associated with a substantial decrease in mortality among frail elderly patients in hospitals.

Lancet January 8, 2000; 355: 93-97 Original investigation, first author William F Carman, University of Glasgow, UK

Comment:

While abstracting this article I wondered if it would be unethical to purposefully withhold flu vaccinations from frail elderly demented individuals.

Alternatively, I believe it would be unethical to expose them knowingly to flu carriers or persons with active infections.

Flu vaccination continues to be underused. The CDC recently lowered the recommended age for routine immunization to 50. Vaccination will spare many healthy young persons a week or two of illness and loss of work. Workers in important public service occupations should also receive vaccine. An editorial in this issue (pp 83-84) suggests that more robust data are needed to establish benefit of immunizing HCW. Meanwhile, I believe it a reasonable intervention, for protection of the HCWs as well as their patients. RTJ

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1-14 URINARY AND SEXUAL FUNCTION AFTER RADICAL PROSTATECTOMY FOR CLINICALLY LOCALIZED PROSTATE CANCER.

To make informed choices about treatment alternatives for prostate cancer (**PC**), physicians and patients need accurate information to assess the potential for, and patterns of, complications.

Numerous investigations have assessed the urinary and sexual function after radical prostatectomy. Reported rates of incontinence varied from 4% to 44%; of impotence from 29% to 75%. Limited data are available to describe the outcomes in unselected population-based patients.

This community-based study in 6 geographic areas measured changes in urinary and sexual function in men who had undergone radical prostatectomy for clinically localized PC.

Conclusion: Radical prostatectomy was associated with significant erectile dysfunction and some decline in urinary function.

STUDY

1. Entered over 1250 men (age range = 39 to 79). All had histologically confirmed localized PC. All underwent radical prostatectomy.
2. Determined urinary and sexual function at baseline, 6, 12, and 24 months.

RESULTS

1. At 18 or more months after surgery, 8% were incontinent and 60% impotent.
2. Among men who were potent at baseline, the proportion reporting impotence at 18 months for various procedures was: non-nerve sparing 66%; unilateral nerve sparing - 57%; bilateral nerve sparing – 56%
3. At 18 months, 42% reported that their sexual performance was a moderate-to-large problem.
4. Urinary and sexual function varied by age: 61% of men < age 60 were impotent at 18 months vs 78% of older men; up to 4% of younger men experienced the highest level of incontinence vs up to 22% of those age 75-79.

DISCUSSION

1. These results are a description of outcomes experienced by a cohort of unselected population-based patients. They are likely to be representative of men in the community as opposed to those reported from single institutions.
2. "Despite significant declines in both urinary and sexual performance levels, most men were satisfied with their treatment choices." And most would choose radical prostatectomy again.

CONCLUSION

Radical prostatectomy was associated with significant erectile dysfunction and some decline in urinary function.

JAMA January 19,2000;283: 354-60 Original investigation by The Prostate Cancer Outcomes Study, first author Janet L Stanford, Fred Hutchinson Cancer Research Center, Seattle, WA.

This demonstrates an important clinical point for primary care clinicians who work in the community and usually refer locally. They cannot rely on the published outcomes from specialized centers to represent local outcomes. They should know the extent of local surgeon's experience (Are they still on the learning curve? How many procedures have they performed? What are their outcomes?)

For men who have had a nerve-sparing procedure, sildenafil (*Viagra*) is some help. RTJ.

1-15 THE VALUE OF PREOPERATIVE MEDICAL TESTING BEFORE CATARACT SURGERY

Routine preoperative testing is commonly performed in patients scheduled for cataract surgery (*and other "minor" surgery*). One study reported the majority of physicians routinely order complete blood counts, serum electrolytes, and ECG. Other tests, chest X-ray, blood-clotting studies, and urinalysis are also ordered, but less often. The value of such testing is uncertain.

This study was designed to determine if routine testing reduces incidence of intraoperative and postoperative medical complications.

Conclusion: Routine testing did *not* increase the safety of cataract surgery.

STUDY

1. Randomly assigned over 18 000 elective cataract patients to be preceded, or not preceded, by a standard battery of tests (ECG, complete blood count, serum electrolytes, urea nitrogen, creatinine and glucose). This was in addition to history taking and a physical examination.
2. Recorded adverse medical events and interventions on the day of surgery and for 7 postoperative days.

RESULTS

1. The most frequent medical events were treatment for hypertension (12 per 1000 operations) and arrhythmia (chiefly bradycardia; 5 per 1000)

2. The overall rate of complications (intraoperative and postoperative combined) was the same in the 2 groups (31 events per 1000 operations).

DISCUSSION

1. Many physicians do not think the tests are necessary, but order them anyway because of institutional requirements, medical legal concerns, or a belief that another physician would want them performed.
2. Most abnormalities in laboratory tests can be predicted from the patient's history and physical exam.
3. Abnormal laboratory tests rarely lead to changes in perioperative treatment.
4. Some studies report that results of laboratory tests are frequently not reviewed and that, when they are abnormal, patients still receive routine intraoperative treatment.
5. Perioperative death or hospitalizations in patients undergoing cataract surgery are very rare. Most medical events occurring during surgery are not serious. It was rarely judged that medical tests would have helped to reduce the risk or severity of any event.
6. The study did not find evidence that preoperative medical testing resulted in postponement or cancellation of surgery.
7. Tests should be ordered only when the history or physical findings would have indicated the test regardless of impending surgery.

CONCLUSION

Routine medical testing before cataract surgery did not increase the safety of the surgery.

NEJM January 20,2000;342:168-75 Original multicenter investigation by the "Study of Medical Testing for Cataract Surgery", first author Oliver D Schein, Wilmer Eye Institute, Johns Hopkins Hospital, Baltimore, MD.

Comment:

I believe there is an important exception to this conclusion. When patients (especially those rarely seen) appear for a pre-surgery consultation, primary care clinicians may ask the patient if he or she wishes to be screened for several abnormalities. For example, a preoperative visit will present the opportunity to screen for impaired glucose tolerance (fasting blood glucose), lipid disorders (lipid screen), hypertension, overweight, and to suggest mammography, and to screen women over age 50 for thyroid disease (sensitive TSH),. Also to ask about any other concerns they may have about their health. RTJ

1-16 POTENTIAL RISK OF CROSS-INFECTION DURING PERIPHERAL-VENOUS ACCESS BY CONTAMINATION OF TOURNIQUETS

Reusable tourniquets for providing venous stasis are carried between many patients and between wards. This practice ". . . contravenes the basic principles of infection control".

This study examined whether reusable tourniquets could act as fomites for microscopic pathogens, thus posing a potential cross-infection risk.

These investigators sampled 50 reused tourniquets of various sorts. They examined the tourniquets for areas of visible blood stains. Twenty five of the 50 were contaminated with blood as confirmed by the Haemoccult test. The places in which the tourniquets were contaminated could easily have contacted the skin.

They then pressed the tourniquets into blood-agar plates for culture. Cultures from all 50 tourniquets grew heavy skin flora; 17 tourniquets grew bacterial pathogens. The investigators thus found a substantial reservoir of potentially pathogenic bacteria on many of these reusable tourniquets.

An additional 27 tourniquets which contained visible blood stains were tested for HIV RNA and Hepatitis B surface antigen. But, neither HIV or HbsAg was detected on any of the 50 tourniquets. However, in areas of high prevalence of HIV and hepatitis B, there is a potential risk of viral transmission.

"We recommend the use of disposable tourniquets."

Lancet January 1, 2000; 355:44 Original investigation, first author M Golder, Kent and Canterbury Hospital, Canterbury, UK

Comment:

Risk would be much greater for the phlebotomist than for the patient. . I would be especially concerned about hepatitis B. RTJ

1-17 ORAL MONTELUKAST COMPARED WITH INHALED SALMETEROL TO PREVENT EXERCISE-INDUCED BRONCHOCONSTRICTION

Exercise-induced bronchoconstriction is common in patients with chronic asthma. Airway cooling and desiccation during exercise may trigger activation of mast cells and release mediators such as histamine and leukotrienes, resulting in bronchospasm.

The long-acting inhaled beta-agonist salmeterol (*Serevent*) protects against exercise-induced bronchoconstriction for up to 12 hours. However, with long-term use, in some patients tolerance to the drug develops and the duration of bronchoprotection diminishes by 6 to 9 hours.

This study compared the oral leukotriene receptor antagonist montelukast (*Singulair*) with salmeterol for protection against exercise-induced bronchoconstriction.

Conclusion: Montelukast protected throughout 8 weeks. Salmeterol lost significant benefits due to development of tolerance.

STUDY

1. Multicenter trial entered 191 adults with asthma. All had documented exercise-induced bronchoconstriction.
2. Randomized double-blind to: 1) montelukast 10 mg once daily in the evening, or 2) salmeterol 50 ug (2 puffs) twice daily.

3. Follow-up = 8 weeks.

RESULTS

1. FEV1 still decreased with exercise for the first 10 to 15 minutes of exercise in both groups, but considerably less so than at baseline. Thereafter, up to 60 minutes after baseline, FEV1 increased in both groups. (*See figure 2 p 100*)
2. By day 3, similar and significant improvements in FEV1 (as compared with baseline FEV1) occurred in both groups.
3. By weeks 4 and 8, the protective effect of salmeterol decreased significantly. The benefit of montelukast persisted.

DISCUSSION

1. With montelukast therapy, bonchoprotection persisted at 8 weeks. In contrast, salmeterol lost much of its benefit, indicating the tolerance had developed.
2. Long-term use, rather than intermittent use, of once-daily oral montelukast for some patients with exercise-induced bronchoconstriction may provide greater protection.

CONCLUSION

The bronchoprotective effects of montelukast against exercise-induced bronchoconstriction were maintained throughout 8 weeks. Salmeterol lost much of its benefit over the same time. Tolerance developed to salmeterol, but not to montelukast.

Annals Int Med January 18, 2000; 132: 97-104 Original investigation by the Exercise Study Group, first author Jonathan M Edelman, Merck and Co., West Point PA, sponsors of the study.

Comment:

The study screened 454 patients and entered 191 (42%). The proportion of those screened who actually enter a study will give some indication of the usefulness of an intervention in clinical practice. The number of patients withdrawing (in this study 6% and 9%) must be added.

Whether montelukast is more effective in individual patients with exercise-induced asthma will depend on the exercise pattern and a trial in each patient. RTJ

1-18 45-YEAR FOLLOW-UP OF HEPATITIS C INFECTION IN HEALTHY YOUNG ADULTS

The long-term outcome of patients with hepatitis C virus (**HCV**) infection is difficult to determine. The initial bout is rarely recognized because of the paucity of symptoms. Even those with established

infections are rarely symptomatic, and end-stage liver disease, when it does occur, takes more than 3 decades to develop.

This cohort study reports results of an extended retrospective of the natural history of HCV using archived serum originally collected decades earlier. Over 8500 military recruits were evaluated for group A streptococcal infection and acute rheumatic fever between 1948 and 1954. Blood taken for the study was kept frozen for almost 45 years.

Seventeen persons had positive results for HCV by enzyme-linked immunosorbent assay and recombinant immunoblot assay. The rate of HVC infection in this cohort paralleled that among present-day military recruits and volunteer blood donors.

During the 45 year follow-up, liver disease occurred 2 of the 17 (12%). Liver disease also occurred in 2.4% of HVC-negative persons. Of the HCV infected persons, one died of liver disease 42 years after the original specimen was obtained. Five died of non-liver related disease at a median of 37 years. (No deaths due to liver cancer occurred in this cohort.)

Over 45 years these HCV positive persons had a low liver-disease related morbidity and mortality. "This suggests that healthy HCV-positive persons may be at less risk for progressive liver disease than is currently thought."

In contrast to this study, retrospective studies of persons who have obvious HCV infections may overemphasize more serious outcomes and may risk omitting persons with subclinical infections as well as those in whom the infection resolves.

Unmistakably, chronic HCV infection is associated with end-stage liver disease. It is the most common cause of liver transplantation. It is possible that HCV infection may progress more slowly when contracted by young healthy persons than by older persons whose health has been compromised. The current concern that progression is common or inevitable may be because most evaluations focus on only a subset of infected persons, usually those who are most seriously affected.

"Progressive liver disease in persons with HCV infection is not inevitable."

Annals Int Med January 18, 2000; 132: 105-11 Original investigation, first author Leonard B Seef, National Institutes of Health, Bethesda, MD

Comment:

I abstracted this article mainly to give primary care clinicians the opportunity to present a more optimistic outlook to patients who may be infected.

For a current review of hepatitis C see "Pathogenesis, Natural History, and Prevention of Hepatitis C" — an NIH Conference. *Annals Int Med* February 15, 2000; 132: 296-305:

"The natural history of hepatitis C continues to be a controversial issue because of the lack of clarification of long-term outcome. Although it is widely accepted that approximately 80% of persons who become infected fail to clear the virus and progress to chronic infection, the uncertain extended outcome had prompted divergent views. Clearly, some infected persons recover completely; some remain HCV viremic without biochemical evidence of liver damage; some seem to have a static form of chronic hepatitis characterized by persistently elevated aminotransferase levels without overt symptoms or disease advancement; some progress over a difficult-to-define period to histological fibrosis and cirrhosis; some have long-term stable cirrhosis identified only through liver biopsy; some have progressive cirrhosis that culminates in liver failure; and finally, some develop hepatocellular carcinoma. The uncertainties lie in the relative frequencies and rates of development of these various sequelae. Indeed, the major questions are whether progression is linear and whether advancements through these increasingly severe manifestations is inevitable."

"Young healthy non-drinking women seem to be at less risk than older alcohol-imbibing men."

"The data suggest that approximately 15% to 20% of persons who acquire HCV infection progress to potentially serious end-stage liver disease, the critical sequela being cirrhosis. The remainder are likely to die of causes other than liver disease."

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REFERENCE ARTICLE

1-19 HERB-DRUG INTERACTIONS

Concurrent use of herbs may mimic, magnify, or oppose the effect of drugs. However, many reports of herb-drug interactions are sketchy and lack laboratory analysis of suspect preparations. Health-care practitioners should caution patients about mixing herbs and pharmaceutical drugs.

Some examples of interactions:

Ginko biloba increases activity of warfarin and may cause bleeding

St John's wort mixed with serotonin-reuptake inhibitors may cause mild serotonin syndrome.

Ginseng mixed with antidepressants may induce mania.

Yohimbine combined with tricyclic antidepressants may increase risk of hypertension.

(*Tables on page 135 and 136 list many clinical reports of interactions.*)

Surveys have reported almost 1 in every 5 adults in the US who regularly take prescription medications concurrently use herbals. The majority do not disclose use to their physicians.

Lancet January 8, 2000;355:134-38 Review article by Adriane Fugh-Berman, George Washington University of Medicine and Health sciences, Washington DC

Comment:

Another adverse effect from use of alternative medicine I learned about recently was related to a patient's use of "chelation therapy" for intermittent claudication. The intravenous injections contained small amounts of heparin. One well known adverse effect of heparin occurs when it complexes with platelets forming an antigen. Platelet destruction follows. This anecdotal patient developed severe thrombocytopenia and bleeding which defied diagnosis until he finally revealed use of this alternative procedure. RTJ

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REFERENCE ARTICLE

1-20 TREATMENT OF ALZHEIMER'S DISEASE

Survival for a decade or more is common after age 65. Prevalence of Alzheimer's disease increases from 3% at age 65 to 47% after age 85.

Criteria for diagnosis are listed on table 1 p 1671. Patients with other causes of dementia (eg, hypothyroidism and cerebro-vascular disease) must be ruled out. Definite diagnosis still depends on postmortem finding of plaques of beta-amyloid and elements of degenerating neurons (neurofibrillary tangles and loss of neurons and synapses) in the brain.

Methodological considerations:

The goals of treatment have been to improve or at least slow the loss of memory and cognition, and to maintain independent function.

The FDA recommends that the outcome of clinical trials should be measured by the Alzheimer's Disease Assessment Scale, Cognitive Subscale. The average score on the cognitive scale worsens by about 8% to 10% annually in untreated patients. The Clinical Interview-Based Impression of Change Scale and the Clinical Global Impression of Change Scale are also recommended as independent multidimensional assessments. (*See table 2 p 1671 for 4 tests used as outcome measures in clinical trials. Citations are listed in the references p 1677-79*)

Cholinergic Augmentation Therapy:

Acetylcholinesterase inhibitors decrease hydrolysis of acetylcholine released by presynaptic neurons. (*See table 3 p 1672 for 6 drug trials of cholinesterase inhibitors*.)

Only 2 drugs are approved in the U.S. – tacrine [*Cognex*] and donpezil [*Aricept*]. They do result in small but measurable benefits in terms of cognitive tests as compared with placebo. Efficacy is limited and is established only for mild to moderate disease. "There is insufficient evidence to recommend that they be given to patients in

nursing homes." Treatment can be continued indefinitely, but it is often discontinued because of decreasing tolerance or lack of effectiveness.

Slowing the Progression of Alzheimer's Disease:

Table 4 p 1674 list 6 studies of various other preparations used including Ginko biloba and vitamin E. None was effective.

Treatment of the Behavioral Manifestations of Alzheimer's Disease

The behavioral manifestations include depression, delusions and psychosis, sleep disturbance, and wandering. *See table 5 p 1676 listing drugs used.* Some have reported benefits. All have adverse effects.

NEJM November 25, 1999; 341: 1670-1679 "Drug Therapy" Review article by Richard Mayeux and Mary Sano, College of Physicians and Surgeons, Columbia University, New York

Comment:

Overall a discouraging outlook. I believe many primary-care clinicians do prescribe donepezil to patients with mild to moderate cognitive impairment. But, don't expect much. RTJ

RECOMMENDED READING

1-21 LOOKING BACK ON THE MILLENNIUM IN MEDICINE

"Medicine is one of the few spheres of human activity in which the purposes are unambiguously altruistic — in itself, a remarkable achievement."

The editorialists restricted themselves to developments that changed the face of clinical medicine (not preventive medicine, public health, health care delivery, or medical ethics). Yet there are obvious overlaps.

They present their choices for the most important medical developments in the last 1000 years. They chose eleven.

Which ones do you choose? I believe most of us would choose many of the same.

NEJM January 6, 2000; 42-49 Editorial by the Editors of *NEJM*