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EDITED BY RICHARD T. JAMES JR. MD

400 AVINGER LANE, SUITE 203

DAVIDSON NC 28036 US

rjames6556@aol.com

HIGHLIGHTS MARCH 2002

3-1 RAPID ANTIBIOTIC DELIVERY AND APPROPRIATE ANTIBIOTIC SELECTION REDUCE LENGTH OF HOSPITAL STAY IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

Rapid delivery of the appropriate antibiotic in the ED was associated with a shorter length of stay in hospitalized patients with community-acquired pneumonia.

Practical point: Primary care clinicians who see very ill patients with infectious disease should administer a full dose of the reasonably appropriate antibiotic immediately in the home, office or emergency department. Do not wait for delivery from the pharmacy or the long door- to-antibiotic time in the hospital. This will improve prognosis.

3-2 PREVALENCE OF IMPAIRED GLUCOSE TOLERANCE AMONG CHILDREN AND ADOLESCENTS WITH MARKED OBESITY

Impaired glucose tolerance is highly prevalent among children and adolescents with severe obesity. It is associated with insulin resistance while beta-cell function is still relatively preserved.

Overt DM2, which occurred in a few adolescents, was linked to beta-cell failure.

Impaired glucose tolerance (2 h pc glucose 126-200) is a more sensitive marker of risk of DM2 than elevated fasting glucose (110-125). This is an important clinical point.

Practical point: Primary care clinicians should maximize efforts to reduce obesity in their adolescent patients.

3-3 EXERCISE CAPACITY AND MORTALITY AMONG MEN REFERRED FOR EXERCISE TESTING

Exercise capacity was a more powerful predictor of increased risk of death than established risk factors such as hypertension, smoking, and diabetes.

Poor fitness is a modifiable risk factor. Improvements in fitness over time have been demonstrated to improve prognosis.

Practical point: Health professionals should incorporate into their practices strategies to promote physical activity at all stages of life. The greatest health benefits are achieved by increasing physical activity among the least fit, including persons without, as well as persons with, cardiovascular disease. Fitness will overcome some of the risks of established risk factors. If you can't stop smoking, at least get fit!

3-4 IMPROVED CARDIORESPIRATORY ENDURANCE FOLLOWING 6 MONTHS OF RESISTANCE EXERCISE IN ELDERLY MEN AND WOMEN

Resistance exercise led to significant improvements in muscle strength, aerobic capacity, and treadmill time in older adults. It is a clinically applicable means of improving fitness. The principal finding of the study was that peak O2 consumption and treadmill time increased in a low-intensity exercise group.

Practical point: Almost all older, non-fit patients, even those with localized muscle weakness, could be instructed to perform some resistance exercises. A program could easily be designed with little equipment and applied at convenient times for variable duration. A formal machine-based program as described in the article would not be necessary. Problems would be motivation and consistency. A successful program would likely enhance balance, and reduce risk of falling.

3-5 BETA-BLOCKERS AND REDUCTION OF CARDIAC EVENTS IN NON-CARDIAC SURGERY

Use of beta blocker therapy perioperatively significantly reduces cardiac morbidity and mortality in patients at high risk.

Practical point: This is an important clinical consideration for primary care clinicians whose patients are contemplating high risk surgery.

3- 6 PARTICIPATION IN COGNITIVELY STIMULATING ACTIVITIES AND RISK OF INCIDENT ALZHEIMER'S DISEASE

Frequent participation in cognitively stimulation activities was associated with reduced risk of cognitive decline and AD.

The frequency of cognitive activity is associated not only with the level of cognition at baseline, but also with the rate of cognitive decline. (*Ie, the rate of cognitive decline even after first stages of AD may be slowed by continuing cognitive activity.)*

If cognitive activity is protective, reduced cognitive activity should be an early sign of disease.

Practical point: Use it, or you will lose it!

3-7 MODERN WORRIES, NEW TECHNOLOGY, AND MEDICINE

Historically, the introduction of new technologies has frequently been accompanied by new complaints, fears, and illness. Currently, the adoption of new technologies is accelerating and is occurring in a climate of suspicion and mistrust in medical evidence. Distrust of experts is now commonplace. At its extreme it can merge into the conspirational thinking that is part of a modern paranoid style. Well publicized crises have clearly dented confidence. Mismanaged environmental incidents and examples of the fallibility of experts are easily recalled.

"It is difficult to feel optimistic." Despite all the evidence of the extraordinary improvements in public health during the past century, surveys show that we experience more symptoms and feel worse than our ancestors." The rapid introduction of new technologies, while improving quality of life, has been accompanied by important adverse effects in the way people make sense of illness and present with health complaints.

Controversy in "scientific" medicine itself compounds the public confusion. Expressions of differences in opinions and conflicting studies published in medical journals quickly reach the media. Is mammography really effective in reducing breast cancer death? Is PCA screening helpful or harmful? What about all the confusion about benefits and harms of hormone replacement therapy? How common are the harms associated with drug therapy and hospitalization?

Practical point: Do you agree? If so, what is to be done?

3-8 STATIN USE, BONE MINERAL DENSITY, AND FRACTURE RISK

Over 2 years, statin use was associated with a 4% absolute reduction in fracture risk . (NNT to benefit one over 2 y = 26)

The protective effect was greater than would be expected from increases in BMD. The mechanism of action is not clear.

Practical point: Many elderly persons will be taking statins for lipid control. Is this an added bonus? Watch for developments.

3-9 HMG COA REDUCTASE INHIBITOR (STATIN) AND AORTIC VALVE CALCIUM

Statin therapy may retard progression of calcific aortic valve disease.

Practical point: Another added bonus?

3-10 LONG-TERM EFFECTS OF MAMMOGRAPHY SCREENING: UPDATED OVERVIEW OF THE SWEDISH RANDOMISED TRIALS

The effect of BC screening in terms of BC mortality reduction persists after long-term follow up. The benefit is highest in women age 55-69 at randomization. The recent criticism against the Swedish trial is misleading and unfounded.

(*By my calculation, screening in the Swedish trial was associated with one death from BC prevented each year for every 1000 women screened. RTJ)*

Practical point: Mammography is so engrained in our society, it would be difficult for primary care clinicians to deny it to their patients.

3-11 PROSPECTIVE STUDY OF MODERATE ALCOHOL CONSUMPTION AND RISK OF HYPERTENSION IN YOUNG WOMEN

The association between alcohol consumption and risk of chronic hypertension in young women followed a J-shaped curve. Light drinkers demonstrated a modest decrease in risk. Regular, more heavy drinkers demonstrated increased risk.

Practical point: The epidemiological evidence for benefits of light drinking is strong and consistent.

3-12 USE OF RAMIPRIL IN PREVENTING STROKE

The ACE inhibitor, ramipril, was associated with a reduced incidence of stroke despite a modest reduction in BP.

Practical point: This is a good example of the "spin" investigators sometimes place on their studies. Their abstract states the relative risk of fatal stroke was reduced by 61%. (In absolute terms this actually amounted to 0.6%; NNT = 166 for 4.5 years to prevent one fatal stroke)

3-13 CARDIOVASCULAR MORBIDITY AND MORTALITY IN LOSARTAN INTERVENTION FOR ENDPOINT REDUCTION IN HYPERTENSION STUDY (LIFE): A Randomized Trial Against Atenolol

The angiotensin II blocker losartan prevented more combined cardiovascular morbidity and death and stroke than the beta-blocker atenolol for a similar reduction in BP. "Losartan seems to confer benefits (*in relation to stroke*) beyond reduction in BP."

Practical point: Another example of "spin" . The benefit of losartan applied to only one person out of 59 over 5 years. This may be "highly significant" statistically, but hardly significant clinically. Primary care clinicians should beware! I believe the conclusions of this study may mislead clinicians who do not have the time to judge the study in detail. Putting a favorable "spin" on conclusions of studies seems to be occurring more frequently.

3-14 DECONSTRUCTING THE PLACEBO EFFECT

The authors of this article present a new perspective to what has been known as the "placebo effect". The most recent serious attempt to try logically to define the placebo effect failed utterly. One definition: "A placebo is a substance or procedure without specific activity for the condition being treated. The placebo effect is the therapeutic effect produced by a placebo." This makes no sense whatsoever. It flies in the face of the obvious. "The one thing of which we can be absolutely certain is that placebos do not cause placebo effects. Placebos are inert and don't cause anything."

The editorialists suggest thinking about this issue in a new way. "Although placebos clearly cannot do anything themselves, *their meaning can*."

3-15 NONSPECIFIC MEDICATION SIDE EFFECTS AND THE NOCEBO PHENONEMON

This article used the nocebo phenomenon to explore the occurrence of adverse, *nonspecific* effects in patients taking active medications and suggest ways in which clinicians can deal more effectively with them.

Practical point: Nocebo and placebo effects accompany all medical interventions. Primary care clinicians accept them even if they do not understand them.

Administer Antibiotics At The Earliest Possible Time

3-1 RAPID ANTIBIOTIC DELIVERY AND APPROPRIATE ANTIBIOTIC SELECTION REDUCE LENGTH OF HOSPITAL STAY IN PATIENTS WITH COMMUNITY-ACQUIRED PNEUMONIA

About 1 million patients are admitted each year with community-acquired pneumonia (**CAP**). It remains the number 1 infectious cause of death. Many studies have documented significant regional variations in length of hospital stay.

This study measured quality-of-care variables relevant to treatment of CAP and determined their relative contributions to variations in length of stay.

Conclusion: Rapid antibiotic administration and appropriate antibiotic selection in the emergency department (ED) were associated with substantial shortening of hospital stay.

STUDY

1. Selected 700 adult patients with pneumonia presenting to Eds. All were judged to require hospitalization.

Patient had to be admitted from the home or a nursing home. Direct to the floor admissions were excluded.

2. The majority had co-morbid conditions.
3. Determined 3 quality-of-care measures: 1) site of initial antibiotic administration (ER or after admission on the floor); 2) door to needle time (apparently all were treated with intravenous antibiotics); 3) appropriate antibiotic selection. (Guidelines defined by the Infectious Disease Society of America [**IDSA**] in 1998.)
4. Determined associations between length of stay in hospital and these variables.

RESULTS

1. All three quality-of-care variables were associated with length of stay. Initial antibiotic given in ED; appropriate antibiotic selection; [1] and shorter door-to-needle time were associated with shorter length-of-stay by a mean of 2 days (7 vs 9).
2. The mean door-to-needle time in the ED was 3.5 hours; on the floor was 9.5 hours.
3. The appropriate choice of antibiotic was especially significant for patients with comorbid conditions.

DISCUSSION

1. Implementation of short door-to-needle time; choice of an appropriate antibiotic; and initial treatment in the ED were associated with shorter hospital stays.
2. A more rapid antibiotic delivery time may hasten the establishment of clinical stability and earlier discharge. This is particularly true of the many elderly high-risk patients with co-morbid conditions who are admitted to the hospital with pneumonia.
3. The choice of optimum antibiotic(s) is important and also may shorten hospital stay. What is the proper choice of antibiotic in patients with community-acquired pneumonia who are judged sick enough to be admitted to the hospital? The article quotes the guidelines issued by the IDSA: [1]
4. In this study many patients were not treated expeditiously in the ED. And many were not treated with an appropriate antibiotic (as defined by the IDSA) in the hospital.

CONCLUSION

Rapid delivery of the appropriate antibiotic in the ED was associated with a shorter length of stay in hospitalized patients with community-acquired pneumonia. There is substantial opportunity for quality improvement.

Archives Int Med March 25, 2002; 162: 682-88 Original investigation, first author David S Battleman, New York Presbyterian Healthcare System. New York, NY **www.archintmed.com**

1 The Johns Hopkins Division of Infectious Diseases has provided an excellent public service web page presenting IDSA guidelines for choice of antibiotics for various infections. [**www.hopkins.abxguide.org**] Recommendations are for patients with community-acquired pneumonia who are considered sick enough to admit. Choice is based on empiric observation, not on randomized trials.

1. Flouroqinolone (alone):

Levofloxacin [*Levaquin*] 500 mg IV or PO daily for 7 to 10 days. or,

Gatifloxacin [*Tequin*] 400 mg IV/PO daily for 7 to 10 days

2. Ceftriaxone [*Rocephin*; 1 g IV daily] or cefotaxime [*Claforan* 1 g IV q 8h] plus a macrolide

A. (Azithromycin [*Zithromax*] 500 mg IV or PO for 5-10 days daily, or

B. Clarithromycin [*Biaxin*] 500 mg PO bid , or

C. Erythromycin 500 mg to 1 g IV q 6h, or 500 mg PO qid

The sickest receive IV medication. All these recommendations are empiric.

Comment:

This is an important clinical application. It reminds me of the British guidelines concerning patients with suspected meningitis seen by primary care clinicians in the home, office or ED. They recommend immediate intramuscular penicillin based on clinical suspicion alone, not waiting for confirmation.

Primary care clinicians are admonished to carry penicillin G in their bags for intramuscular use in the home, not waiting for hospital admission.

The same approach is also important for sick patients with community-acquired pneumonia. I believe primary care clinicians should administer an appropriate antibiotic immediately. Waiting for administration of the hospital floor entails: first, getting admitted; then reviewing the order; ordering the drug from the pharmacy; waiting for delivery; and waiting for the drug cart to make rounds. This process, as noted in the study, may take over 8 hours. Meanwhile the patient is getting sicker.

It would be appropriate for clinicians to keep a supply of antibiotics readily available. Would not immediate administration of a reasonably appropriate antibiotic given by mouth be a significant therapeutic measure for a sick, elderly outpatient?

The usual recommendations for hospital admission include advanced age, admission from a nursing home, mental confusion, comorbidity, respiratory rate above 30, BP less than 90 systolic or 60 diastolic, hypoxemia (O2 saturation less than 92% on pulse oximetry. RTJ

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This National Health Hazard Threatens The Health Of Millions. Treat It Early

3-2 PREVALENCE OF IMPAIRED GLUCOSE TOLERANCE AMONG CHILDREN AND ADOLESCENTS WITH MARKED OBESITY

The epidemic of childhood obesity in the US has been accompanied by a marked increase in frequency of type 2 diabetes mellitus (**DM2**). DM2 develops over a long period. Most individuals, if not all, initially have impaired glucose tolerance (**IGT**). IGT is an intermediate stage in the natural history of DM2. It predicts the risk of development of DM2 and cardiovascular disease. With appropriate changes in lifestyle, progression from IGT to DM2 can be delayed or prevented. Great emphasis has been placed on early detection of IGT in adults.

This study determined risks of DM2 in obese children and adolescents. Does obesity at this age lead to IGT?

Conclusion: IGT was highly prevalent among children and adolescents with severe obesity.

STUDY

1. Recruited 55 obese children (age 4 to 10) and 112 adolescents (age 11 to 18). All had a body mass

index (**BMI**) higher than the 95th percentile for their age and sex. [Mean BMI children = 32; adolescents = 35.]

2. Approximately 40% of the 58 adolescent girls had hirsutism, oligomenorrhea, acne, and increased testosterone, suggesting polycystic ovary syndrome. [1]
3. Administered an oral glucose tolerance test with a dose of 1.75 g per kg up to a maximum of 75 g.

Determined plasma glucose, insulin, and C-peptide every 30 minutes for 2 hours. Defined IGT as fasting glucose less than 126 mg/dL and a 2-h glucose between 140 and 200. Defined DM2 as fasting glucose 126 or higher, or 2-h glucose more than 200. [*Impaired fasting glucose is defined as between 110 and 125. RTJ*]

RESULTS

1. IGT was detected in 25% of the children and 21% of the adolescents.
2. Insulin and C-peptide were markedly elevated in those with IGT. But not in the adolescents with DM2.
3. Insulin resistance was greater in those with IGT.
4. Silent DM2 was identified in 4 adolescents.

DISCUSSION

1. In these obese children and adolescents, there was a high prevalence of IGT. Frank DM2 was discovered in a few adolescents. (*Ie, DM2 can occur in childhood.)*
2. Risk factors for IGT included insulin resistance, marked hyperinsulinemia fasting, and after a glucose challenge, and hyper pro-insulinemia. [2]
3. Look for signs of polycystic ovary syndrome in adolescent girls with IGT.
4. The onset of IGT was clearly associated with development of insulin resistance while beta-cell function was still relatively preserved.
5. In the 4 with DM2, insulin secretion declined and disproportionate hyper-pro-insulinemia was present. "Disproportionate hyper-pro-insulinemia is a clear marker of beta-cell dysfunction in overt type 2 diabetes." "The vigorous hyper-pro-insulinemic response to glucose found in the pre-diabetic stage in obese children and adolescents may reflect an up-regulation of beta-cell function caused by chronic severe insulin resistance."
6. In these obese children and adolescents with IGT, prevalence of impaired fasting glucose (110 to 125 mg/dL) was low (less than1%). "Fasting hyperglycemia is indicative of a more advanced stage of clinical diabetes and the determination of its presence represents a very insensitive method for detecting impaired glucose tolerance." [3]

CONCLUSION

Impaired glucose tolerance is highly prevalent among children and adolescents with severe obesity. It is associated with insulin resistance while beta-cell function is still relatively preserved.

Overt DM2, which occurred in a few adolescents, was linked to beta-cell failure.

NEJM MARCH 14, 2002; 346: 802-10 Original investigation, first author Ranjana Sinha, Yale University School of Medicine, New Haven, Conn. **www.nejm.org**

An editorial in this issue (pp 854-55) comments:

Childhood obesity is directly linked to abnormalities of BP, lipids, insulin levels, and risk of both coronary heart disease and diabetes. One study of obese adolescents documented that 80% had elevated BP, almost all had 4 or more risk factors: elevated triglycerides, low HDL-cholesterol, increased total cholesterol, elevated BP, and a strong family history of coronary disease, myocardial infarction, angina, and high BP.

In the preceding study, 2 of 3 subjects with IGT followed for 2 to 5 years developed frank diabetes.

Comment:

1 The polycystic ovary syndrome (also called Stein-Leventhal syndrome or sclero-cystic disease of ovary) is characterized by increased androgen production by the adrenal.

2 I had to refresh my memory about the terminology of insulin production. Proinsulin is a precursor of insulin. It is a long single-chain peptide of 116 amino acids. There are 3 subdivisions: The A chain contains 21 amino acids; the B chain contains 30; a connecting peptide (C-peptide) of 65 amino acids connects A and B. To form active insulin, the C-peptide is split off and the A and B chains connect with difulfide bonds.

3 Impaired glucose tolerance (2 h pc glucose 126-200) is a more sensitive marker of risk of DMS than impaired fasting glucose (110-125). This is an important clinical point. RTJ

A More Powerful Predictor Of Death Than Other Risk Factors.

3-3 EXERCISE CAPACITY AND MORTALITY AMONG MEN REFERRED FOR EXERCISE TESTING

Exercise capacity is an important prognostic factor in mortality of patients with cardiovascular disease. This study asked: Does exercise capacity predict mortality equally well among healthy persons as among those with cardiovascular disease?

Conclusion: Exercise capacity was a more powerful predictor of death than other established risk factors among normal men as well as among those with cardiovascular disease.

STUDY

1. Studied over 6000 consecutive men referred for treadmill exercise testing for clinical reasons. (Mean age = 58)
2. Classified them into 2 groups: 1) those with an abnormal exercise test or a history of cardiovascular disease, or both; 2) those with a normal exercise test and no history of cardiovascular disease. (N over 2500)
3. Follow-up = a mean of 6 years. End-point = overall mortality.

RESULTS

1. There were over 1200 deaths during follow-up (20% of cohort).
2. Men who died were older, had a lower maximal heart rate, lower maximal systolic and diastolic BP, and lower exercise capacity measured as metabolic equivalents (**METs**).

3. After adjustment for age, the peak maximal exercise capacity measured in METs was the strongest predictor of the risk of death among normal men as well as those with cardiovascular disease. Each MET increase in exercise capacity conferred a 12% improvement in survival.
4. Among subsets of patients with hypertension, COPD, diabetes, smokers, obesity, and elevated total cholesterol, those with the highest exercise capacity (> 8 METS) had about a 50% lower risk of death from any cause than those with capacity < 5 METS. A near linear reduction in death occurred as fitness levels increased.
5. For each quintile of exercise capacity, the relative risk of death increased as the METs achieved decreased.
6. There was no interaction between the use of beta-blockers and the predictive power of exercise capacity.

DISCUSSION

1. The study afforded the opportunity to assess normal subjects as well as those with cardiovascular disease. Exercise capacity was a similarly important marker of risk in both groups.
2. The maximal exercise testing used in this study provided an objective measure of physical fitness.
3. In healthy subjects (as well as those with cardiovascular disease) the peak exercise capacity achieved was a stronger predictor of increased risk of death than established risk factors such as hypertension, smoking, and diabetes.
4. Poor fitness is a modifiable risk factor. Improvements in fitness over time have been demonstrated to improve prognosis. Health professionals should incorporate into their practices strategies to promote physical activity. The greatest health benefits are achieved by increasing physical activity among the least fit, including both persons without, as well as persons with, cardiovascular disease.
5. Outcomes were not affected by beta-blockade. Among those taking beta-blockers, the most fit were the most likely to survive.

CONCLUSION

Exercise capacity was a more powerful predictor of mortality than other established risk factors (such as hypertension, smoking, and diabetes) for cardiovascular disease in normal men as well as in men with cardiovascular disease.

NEJM March 14, 2002; 346: 793-801 Original investigation, first author Jonathan Myers, Stanford University Medical Center, Palo Alto, California**. www.nejm.org**

Comment:

One MET is the oxygen uptake when a person is at rest. — about 3.5 mL of O2 per kilogram of weight per minute.

Fitness will overcome some of the risk in persons with established risk factors. If you can't stop smoking, at least get fit! RTJ

Benefits Elders Who Cannot Exercise Aerobically

3-4 IMPROVED CARDIORESPIRATORY ENDURANCE FOLLOWING 6 MONTHS OF RESISTANCE EXERCISE IN ELDERLY MEN AND WOMEN

Interventions to improve cardiorespiratory endurance have important health implications. Endurance exercise is traditionally viewed as the primary means of increasing aerobic capacity. Resistance exercise, in contrast, is not typically viewed as a means of improving cardiorespiratory fitness.

This study examined the effects of resistance exercise on aerobic capacity in elderly subjects.

Conclusion: Resistance exercise led to significant improvements in aerobic capacity.

STUDY

1. Followed 62 men and women volunteers aged 60 to 83 (mean = 68) to completion of a six month course of resistance exercise.
2. One third were controls; 1/3 assigned to low-intensity resistance exercise; 1/3 to high-resistance exercise. (*I omit the high-intensity group because compliance with this degree of effort would not be routinely acceptable to primary care patients in this age group. RTJ*)
3. Subjects were tested by determining their maximum strength in 8 resistance exercises beginning with light weight lifting and incrementally increasing the load up to a maximum. The low-intensity group then exercised at 50% of this maximum.
4. Over 6 months, eight different resistance exercises were performed on an exercise machine in single sets of 13 repetitions with a 2 minute rest between. All attended at least 85% of the thrice-weekly sessions.

RESULTS

1. At 6 months, maximum strength increased significantly in low-intensity group.
2. Aerobic capacity (peak O2 consumption tested on a treadmill) increased by 24% compared to controls.
3. Treadmill time to exhaustion increased by 26%.

DISCUSSION

1. The principal finding of the study was that peak O2 consumption and treadmill time increased in the low-intensity exercise group.
2. It is reasonable to conclude that endurance performance during submaximal activities of daily living would also benefit.
3. Resistance training may be a viable means of improving cardiorespiratory endurance in elderly persons. Improvement might be greater in those who are more deconditioned and frail, or when recovering from an illness.

CONCLUSION

Resistance exercise led to significant improvements in muscle strength, aerobic capacity, and treadmill time in older adults. Peak O2 consumption and treadmill time increased in a low-intensity exercise group.

Archives Int. Med March 25, 2002; 162: 673-78 Original investigation, first author Kevin R Vincent, College of Medicine, University of Florida, Gainesville **www.archinternmed.com**

Comment:

Many elders cannot perform aerobic exercise. Almost all patients, even those with localized muscle weakness, could perform some resistance exercises. I believe resistance exercise is a clinically applicable means of improving fitness. A program could be designed with little equipment and applied at convenient times for variable duration. A formal machine-based program as described in the article would not be necessary. Problems would be motivation and consistency. A successful program would likely enhance balance and reduce risk of falling. RTJ

An Important Practical Preventive Measure

3-5 BETA-BLOCKERS AND REDUCTION OF CARDIAC EVENTS IN NON-CARDIAC SURGERY

Cardiac events such as myocardial infarction (**MI**) and cardiac death occur in over 1% of unselected patients undergoing major non-cardiac surgery.

This study asks: Does beta-blockade given perioperatively reduce the risk of these adverse events?

Conclusion: Beta-blockade prevents perioperative cardiac morbidity.

STUDY

1. Performed literature search related to perioperative cardiac complications and beta-blockade.
   Selected 5 prospective randomized studies which assessed the impact of beta-blockade on cardiac ischemia, MI, and mortality in patients undergoing major non-cardiac surgery.
2. Beta-blockers included atenolol, bisoprolol, esmolol, and labetolol.
3. All sought to achieve beta-blockade before induction of anesthesia by titrating dose to a target heart rate.
4. The studies included patients with evidence of prior coronary disease, risk factors for CHD, and untreated hypertension

RESULTS

1. For prevention of myocardial ischemia, the number needed to treat (NNT) to prevent one event varied between 3 and 7. For mortality, cardiac or all cause, the NNT was 3 to 8.
2. The most marked benefits were seen in patients at high risk. For those at highest risk the NNT was as low as 3.
3. Adverse effects: One study reported a high rate of bradycardia which required atropine therapy.
   Patients who discontinued perioperative use immediately after surgery had a marked increase in MI after surgery.
   "Discontinuing beta-blocker use in patients who have a longstanding indication for adrenergic blockade may lead to adverse outcomes perioperatively, and worsen survival.
4. Who should receive beta-blockers perioperatively?

Patients at low risk can be excluded, especially those undergoing low-risk procedures. Harms may outweigh benefits. Patients at high risk should receive beta-blockade:

High risk surgical procedure — intraperitoneal, intrathoraccic or suprainguinal vascular procedure.

History of ischemic heart disease

History of cerebrovascular disease

Chronic renal insufficiency (creatinine > 2.0 mg/dL)

Diabetes requiring insulin

Congestive heart failure is a high risk, but not an indication for immediate perioperative beta-blockade.

For the many patients taking beta-blockers long before the immediate perioperative period, including those with congestive failure, it is important to continue.

Beta-blockade may have additional benefits in elderly patients.

Which beta-blocker to use?

All studies showing benefit have used Beta-1 (heart) selective agents, with no advantage found for any particular one. Propanolol (non-selective) may have adverse effects on lung function.

When to start prophylaxis? When to discontinue?

Start early enough to achieve sympatholysis. Doses should be titrated appropriately. In some cases intravenous atenolol has been given intravenously to titrate dose in the pre-anesthesia holding area. The short-acting agent esmolol may be used. The article suggests titrating to a heart rate of 65 or less. Postoperatively, continue at least through hospitalization, giving intravenously if oral therapy is not feasible. Most studies continued for up to a month. In select patients continue indefinitely. The occasion may encourage prescription of long-term therapy in patients who should have been receiving it.

If long-term therapy is not warranted, the dose should be tapered off.

CONCLUSION

Use of beta blocker therapy perioperatively significantly reduces cardiac morbidity and mortality in patients at high risk.

JAMA March 20, 2002l 287: 1435-44 Scientific review, first author Andrew D Auerbach, University of California, San Francisco**. www.jama.com**

Comment:

This is an important clinical consideration for primary care clinicians whose patients are contemplating high risk surgery. RTJ

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If You Don't Use It, You Lose It!

3-6 PARTICIPATION IN COGNITIVELY STIMULATING ACTIVITIES AND RISK OF INCIDENT ALZHEIMER'S DISEASE

Does frequent participation in cognitively stimulating activities reduce risk of Alzheimer's disease (**AD**)? This has been hypothesized, but not tested prospectively.

This study used an established measure of frequency of participation in common cognitive activities and tested its association with incidence of AD and decline in cognitive function.

Conclusion: Frequent participation in cognitively stimulating activities was associated with reduced risk of Alzheimer's disease.

STUDY

1. Longitudinal cohort study followed over 700 Catholic nuns, priests, and brothers older than age 65.
2. None had dementia at baseline.
3. Participants rated frequency of participation in common cognitive activities. At baseline asked about 7 common activities which involve information processing: viewing TV, listening to radio, reading newspapers, reading magazines, reading books, playing games (eg, checkers, cards, crossword and other puzzles), and going to museums.
4. Rated frequency of participation in each activity on a 5-point scale: daily – 5 points; several times a week – 4 points; several times a month - 3 points; several times a year – 2 points; once a year or less – 1 point.
5. Repeatedly tested for cognition over a mean of 4.5 years. At each evaluation, administered 20 tests of cognition. (*See text p 743*) Criteria for diagnosis of AD required a history of cognitive decline, and impairment of memory and at least one other cognitive domain.
6. A neurologist made a clinical diagnosis of AD based on national standard criteria, assessed change in global and specific measures of cognitive function, and compared cognitive activity score change with baseline.

RESULTS

1. Baseline scores on the composite measure of cognitive activity ranged from 1.6 to 4.7. (Higher scores indicate more frequent activity.)
2. During follow-up, 111 persons developed AD.
3. After controlling for age, sex, and education, a 1-point increase in cognitive activity score was associated with a 33% reduction in risk of AD.
4. A 1-point increase in cognitive activity score was associated with a 30% to 60% slower decline in global cognition, working memory, and perceptional speed.
5. Physical activity was *not* related to rate of decline of cognition.

DISCUSSION

1. On average, during 4.5 years, a person reporting frequent cognitive activity at baseline had about half the risk of developing AD as a person with little cognitive activity.
2. "These results suggest that frequent cognitive activity in old age is associated with reduced risk of incident AD."
3. This study found, as have others, that the frequency of cognitive activity is associated not only with the level of cognition at baseline, but also with the rate of cognitive decline. (*Ie, the rate of cognitive decline even after first stages of AD may be slowed by continuing cognitive activity.)*
4. If cognitive activity is protective, reduced cognitive activity should be an early sign of disease.

CONCLUSION

Frequent participation in cognitively stimulation activities was associated with reduced risk of cognitive decline and AD.

JAMA February 13, 2002; 287: 742-48 Original investigation, first author Robert S Wilson, Rush-Presbyterian-St Luke's Medical /Center, Chicago, IL **www.jama.com**

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Public Suspicion Remains High

3-7 MODERN WORRIES, NEW TECHNOLOGY, AND MEDICINE

"Over the years, there has been a steady and important change in the public's perception of the relation between aspects of modern life and health. At the beginning of the 21st century, people's suspicion of modernity has increased to such an extent that it has undermined their view of their own health, increased their worries about environmental causes of poor health, and fostered a migration to complementary medicine. Concerns about safety of mobile phones, environmental pollution, vaccines, bovine spongioform encephalopathy, genetically modified food, and food in general have led to a heightened awareness of the effect of environmental changes on health. We believe that these concerns, which have been largely unrecognized by researchers, have important implications for the way patients interact with health services. Public suspicion remains high."

In clinical settings, patients are reluctant to start medication or to continue for an extended period for fear of putting "unnatural chemicals" into their body. At the same time the consumption of unproved herbal and alternative "natural" remedies is increasing.

The number of illnesses attributed to environmental factors (eg, sick building syndrome, chemical sensitivity, total allergy syndrome) has increased.

An increase in the public's fascination with personal health and medicine has fostered this unease with modernity. The media's increased coverage of health topics has raised worries about routine health care, and increased people's perception of their vulnerability to new and exotic illnesses. Media stories tend to misrepresent

the dangers of new environmental influences and aspects of modernity, while playing down more mundane causes of ill health such as the link between tobacco and heart disease.

This deluge of information on the supposedly pervasive risks to personal health has made people feel much more vulnerable. Normal everyday symptoms such as headache and fatigue are now more easily interpreted as signs of disease or ill health. Patients see the effects of modern life as undermining the efficacy of their immune system. Persons who are most concerned about the effects of modern life on health are more likely to complain of symptoms, have more functional illness, and be consumers of complementary health care.

Historically, the introduction of new technologies has frequently been accompanied by new complaints, fears, and illness. Currently, the adoption of new technologies is accelerating and is occurring in a climate of suspicion and mistrust in medical evidence. Distrust of experts is now commonplace. At its extreme it can merge into the conspirational thinking that is part of a modern paranoid style. Well publicized crises have clearly dented confidence. Mismanaged environmental incidents and easily recalled examples of the fallibility of experts, such as the cases of new variant Creutzfeldt-Jacob disease and thalidomide, add to the fears of the public and undermine trust. “Sadly, trust once lost is difficult to restore.”

The internet has brought a new dimension to the spread of worries and health scares. New and unsubstantiated health worries are instantly transmitted to an audience eagerly seeking information on health, or to special interest networks and illness support groups. “We believe it is only a matter of time before a mass psychogenic illness is identified as being spread electronically.”

“It is difficult to feel optimistic.” Despite all the evidence of the extraordinary improvements in public health during the past century, surveys show that we experience more symptoms and feel worse than our ancestors. The

rapid introduction of new technologies, while improving quality of life, has been accompanied by important adverse effects in the way people make sense of illness and present with health complaints.

BMJ March 23, 2002; 324: 690-91 Editorial, first author Keith J Petrie,, University of Auckland, New Zealand.
www.bmj.com

Comment:

I believe the editorialists overstate their case to some extent.

Patients present a paradox in their feelings about modern scientific medicine. Many distrust the system. Yet, if asked if they like and trust their personal physician, they reply “Yes I do”. All clinical applications have a one-to-one patient-doctor relation. That patients trust their individual physicians and mistrust the system seems to me to be paradoxical.

At the same time a large percentage of patients will use complementary-alternative medicine (**CAM**) without informing their physician – sort of a mistrust in reverse.

Patients may seek more reassurance and support than their personal physician gives them. In this respect we often fail. Patients then fly to solace in CAM, which they seem to trust.

Controversy in “scientific” medicine itself compounds the public confusion. Expressions of differences in opinions and conflicting studies published in medical journals quickly reach the media. Is mammography really effective in reducing breast

cancer death? Is PCA screening helpful or harmful? What about all the confusion about benefits and harms of hormone replacement therapy? How common are the harms associated with drug therapy and hospitalization?

No wonder that primary care practice is so difficult. RTJ

Another Benefit Of Statins?

3-8 STATIN USE, BONE MINERAL DENSITY, AND FRACTURE RISK

Recent data suggest that statins used in treatment of hypercholesterolemia increase bone mineral density (**BMD**) and decrease fracture risk.

This study evaluated the association between statin use and BMD and fracture risk in women.

Conclusion: A substantial reduction in fracture risk was associated with statin use.

STUDY

1. Cross-sectional study in Australia evaluated association between statin use and BMD in over 1300 women (age 50-95; mean = 70).
2. Determined current statin use in over 550 women who developed fracture during a 2-year period and over 800 women who did not experience a fracture.
3. Self-reported questionnaire assessed diet and lifestyles and statin use.
4. Determined BMD.

RESULTS

1. There were 16 statin users in the fracture group (2.7%) and 53 statin users in the non-fracture group (6.6%).
2. Absolute fracture difference between groups = 3.9%. (NNT to benefit one over 2 y = 26)
3. BMD at the femoral neck was 3% greater in statin users.
4. BMD also tended to be greater in the spine and whole body (not statistically significant).

DISCUSSION

1. Statin use was associated with a reduction in risk of fracture. The reduction was not wholly explained by the effects on BMD. (The increases in BMD were too small to account for the effect.)
2. Other case-control studies in different populations have also reported a reduction in risk among statin users. There is an exception: pravastatin (*Pravachol*) has been reported to have no effect on fracture. It may have less effect on increasing BMD.
3. The mechanism of action remains unclear.

CONCLUSION

Over 2 years, statin use was associated with an absolute reduction in fracture risk of 4%. (NNT to benefit one over 2 y = 26)

The protective effect was greater than would be expected from increases in BMD. The mechanism of action is not clear.

Arch Int Med March 11, 2002; 162: 537-40 Original investigation first author Julie a Pasco, University of Melbourne, Geelong Hospital, Australia. **www.archinternmed.com**

Comment:

I abstracted this article as a possible added benefit of statins. Certainly not to be used for this purpose. Watch for additional studies.

Still Another Benefit?

3-9 HMG COA REDUCTASE INHIBITOR (STATIN) AND AORTIC VALVE CALCIUM

Aortic valve sclerosis, defined as thickening and calcification of the trileaflet aortic valve without obstruction to outflow, is a common disease in the elderly. Progressive leaflet calcification and fibrosis can lead to obstruction of left ventricular outflow (stenosis). At present no pharmacological therapy has been shown to decrease the rate of leaflet calcification.

Aortic valve calcification (**AVC**) occurs in areas of lipoprotein deposition. Raised LDL-cholesterol is associated with increased risk of aortic sclerosis.

Electronbeam computed tomography (**EBT**) has been used to quantify coronary artery calcification. It also is a highly reproducible method of quantifying AVC.

Statin drugs have been associated with a decrease in coronary calcification. Might EBT be used to indicate an association between statins and AVC accumulation?

This retrospective analysis entered over 600 asymptomatic patients referred for EBT scanning to assess coronary artery calcium accumulation. All received 2 consecutive EBT scans at least 6 months apart (mean = 2.5 years). Identified 65 patients with aortic valve calcification. Twenty eight (43%) were receiving statins at the time of both scans. Statin therapy was associated with 63% lower rate of ACV accumulation. Median increase in AVC rates was

28% per year in the no-statin group vs 11% in the statin group.

This suggests that statin therapy may favorably alter the natural history of calcific aortic valve disease.

Lancet March 30, 2002; 359: 1125-26 Original investigation, first author David M Shavelle, University of Washington, Seattle **www.thelancet.com**

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Does This Settle The Controversy?

3-10 LONG-TERM EFFECTS OF MAMMOGRAPHY SCREENING: UPDATED OVERVIEW OF THE SWEDISH RANDOMISED TRIALS

There has been much debate about the value of screening mammography.

This study updates the overview of Swedish randomized controlled trials up to 1997. It contains data from trials that have not been presented before.

Conclusion: Beneficial effects of mammographic screening on breast cancer (**BC**) mortality persist after long-term follow-up. Recent criticism of the Swedish trials is misleading and scientifically unfounded.

STUDY

1. The 5 trials included over 247 000 population-based women — 129 000 invited to receive mammography, and a control group of 117 000. Age at entry varied between 38 to 75. Attendance rate varied from 74% to 89%.
2. Followed up by the Swedish Cancer and Cause of Death Registers. Calculated the relative risks (**RR**) for BC death between groups.

RESULTS

1. The median time from randomization to the end of follow-up was 16 years.
2. Breast cancer deaths occurred in 511 women (1 864 770 women-years) in the mammography group and 584 (1 688 440 women-years) in the control group. (*By my calculation, this is equivalent to 2.7 women per year per 1000 screened and 3.5 per year per1000 women in the control group. RTJ*)
3. This was a significant 21% reduction in BC mortality in the screened group. (RR = 0.79).
4. Reduction was greatest in the age group 60-69 at entry. Significant reductions occurred in all groups 55-69. There was a small effect in women 50-55 at randomization (RR = 0.95). Benefit was also present in the 40-49 decade.
5. The benefit in terms of cumulative BC mortality began to emerge at about 4 years after randomization and continued to increase to about 10 years. Thereafter the benefit in absolute terms was maintained throughout the period of observation,.

DISCUSSION

1. “Our main observation was that the benefit of screening was maintained for several years after the trials had been
closed. In general the benefit in absolute terms increased up to 12 years after randomization and thereafter it was maintained.”

CONCLUSION

The effect of BC screening in terms of BC mortality reduction persists after long-term follow up. The benefit is highest in women age 55-69 at randomization.

The recent criticism against the Swedish trial is misleading and unfounded.

Lancet March 16, 2002; 359: 909-19 Original investigation, first author Lennarth Nystrom, Umea University, Sweden **www.thelancet.com**

An editorial in this issue of Lancet (pp 904-05) comments:

"Last year at an oncology meeting in Cambridge (UK), a 53 year old American journalist confessed that she had not yet had a mammogram because she could not get a clear answer about its usefulness. She had read the research studies, talked to doctors on both sides of the Atlantic on both sides of the debate, and was still baffled" She is not alone. The literature on screening provides ample opportunity for confusion and dogma. It can be interpreted to prove both benefit and harm. Is there a clear answer? The preceding study gives further information.

The benefits of BC screening appear real but modest. Overall (all cause) mortality showed a relative risk of just 0.98 between the invited and the control groups. This small effect is not surprising for a disease that contributes only modestly to overall mortality.

The natural history of BC is such that avoiding death from BC can be measured only after many years or decades after the start of screening. Confirmation of the stability of the reductions in BC mortality over time is perhaps the most useful contribution of the paper.

Comment:

By my calculation, screening in the Swedish trial was associated with one death from BC prevented each year for every 1000 women screened. RTJ

Another Benefit Of One Drink A Day

3-11 PROSPECTIVE STUDY OF MODERATE ALCOHOL CONSUMPTION AND RISK OF HYPERTENSION IN YOUNG WOMEN

Heavy alcohol consumption is strongly associated with increased risk of hypertension. About 5% of high BP in women is attributable to heavy alcohol consumption. Light-to-moderate consumption, has been associated with a reduced risk of ischemic stroke and coronary heart disease among women.

This study asks — what are the effects of light-to-moderate consumption on the BP of young women?

Conclusion: The association between alcohol consumption and risk of chronic hypertension in young women followed a J-shaped curve. There was a modest decrease in risk in those drinking light-to-moderate amounts.

STUDY

1. The Nurses' Health Study prospectively examined the association between alcohol consumption

and incident hypertension among over 70 000 women age 25 to 42 (mean = 35) at baseline.

2. Questionnaires every 2 years asked about average alcohol intake (beer, wine, or liquor) during the past year.
3. They were asked about development of physician-diagnosed hypertension (> 140/90).
4. Follow-up = 8 years.

RESULTS

1. During 8 years over 4000 cases of incident hypertension (6% of cohort) were reported.
2. After adjustment, the association between alcohol consumption and risk of hypertension followed a J-shaped curve.
3. Compared with abstainers, the relative risk of developing hypertension according to number of drinks consumed per day:

0.25 or less	0.96
0.26 to 0.500.86	
0.51 to 1.000.92	
1.01 to 150	1.00
151 to 2.00	1.20
More than 2	1.31

4. Among women in the highest category of consumption, the increased risk occurred regardless of the type of alcohol consumed.
5. Binge drinking (consumption of more than 10 drinks over 3 or fewer days per week) was not associated with increased risk of hypertension.

DISCUSSION

1. "In this study of 70891 women, the association between alcohol intake and risk of hypertension followed a J-shaped curve."
2. Among women who consumed 0.26 to 0.5 drinks daily the risk was lower by 14% compared to abstainers. Among women who consumed 1 drink daily the risk was lower by 8% compared to abstainers.
3. An increased risk of hypertension was evident beyond consumption of 1.5 drinks per day.
4. No beverage-specific effect was noted.
5. Although episodic (binge) drinking may have been associated with acute elevation of BP, in this study it was not associated with chronic hypertension unless heavier consumption extended to most days of the week.
6. Among women who consumed up to 25 or more drinks per week before onset of the study, no noticeable elevated risk of hypertension was evident during the study. This suggests that the ill effects of heavy past drinking do not persist.

CONCLUSION

The association between alcohol consumption and risk of chronic hypertension in young women followed a J-shaped curve. Light drinkers demonstrated a modest decrease in risk. Regular more heavy drinkers demonstrated increased risk.

No beverage-specific effect was noted.

Archives Int Med March 11, 2002; 162: 569-74 Original investigation, first author Ravi Thadhani, Brigham and Women's Hospital, Boston Mass. **www.archintmed.com**

Comment:

The epidemiological evidence of alcohol consumption has been remarkably consistent for years. Light consumption (one drink a day on average) is associated with multiple health benefits. Most studies do not report any specific benefit from the type of alcohol. "A votre sante" RTJ

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Beware Of "Spin" Put On Conclusions

3-12 USE OF RAMIPRIL IN PREVENTING STROKE

Strokes can be prevented by lowering BP in hypertensive patients, and by antiplatelet agents in people with vascular disease. Although a person's risk of stroke increases with BP, the population attributable risk of stroke is greatest at pressures which would currently not be treated with drugs. Additional strategies that lower risk of stroke across a broad range of patients are needed.

Angiotensin-converting enzyme inhibitors (**ACE**) block the activation of the renin-angiotensin system in the vascular wall as well as in the plasma. They may have a range of other actions. (Eg, reduce proliferation of vascular smooth muscle; enhance fibrinolysis; stabilize plaques; decrease plaque rupture.) ACE have the potential to lower risk of ischemic vascular events through mechanisms independent of lowering BP.

This secondary assessment of an original trial assessed the effect of the ACE ramipril [*Altace*] on secondary prevention of stroke.

STUDY

1. Randomized controlled trial entered over 9000 patients. All were over age 55 (mean = 66) and considered at high risk for cardiovascular events because of history of cardiovascular disease and continuing risk factors and diabetes.
2. Mean BP at baseline = 139/79. (46% were considered to have hypertension.)
3. The majority (76%) were taking aspirin; 28% taking lipid-lowering agents.
4. Randomized to:
   1) Ramipril 10 mg daily
   2) Vitamin E 400 IU daily (*I omit this data — not beneficial. RTJ*)
   3) Both
   4) Placebo

5. Outcome measures: stroke, TIA, cognitive function. (*The primary endpoint in the original study was a composite of myocardial infarction, stroke, or cardiovascular death.)* This *subset* of the study

focuses on stroke.

6. Follow-up - 4.5 years.

RESULTS

Ramipril vs placebo:

1. Reduction in BP was modest (mean of 3.8/2.8 mm Hg)

2. Absolute risk reductions:	NNT 4.5 years to benefit one
Any stroke = 1.5%	66
Fatal stroke = 0.6%	166
Combined risk of stroke and TIA = 1.9%	53
Change in cognition = 0.5%	200

DISCUSSION.

1. "Our results show that prolonged treatment with ramipril is effective in reducing fatal and non-fatal stroke and transient ischemic attack in a broad group of patients at high risk of stroke but with a relatively normal blood pressure."
2. Benefit was independent of the modest reduction in BP with ramipril.
3. Benefit was seen in all values of BP including patients with an initial BP less than 120/70. Benefit was not confined to those with "high BP".
4. “Our results indicate that patients who are at high risk of stroke should be treated with ramipril irrespective of their initial blood pressure and in addition to other preventive measures.” [1]

CONCLUSION

Ramipril was associated with a reduced incidence of stroke despite a modest reduction in BP.

BMJ March 23, 2002; 324: 699-702 Original investigation, first author Jackie Bosch, McMaster University, Hamilton, Ontario. Canada. **www.bmj.com/cgi/content/full/324/7339/699**

Comment:

1 Do the investigators overstate their case? I believe so. This is a good example of the “spin” investigators and drug companies sometimes place on their studies. Their abstract states the relative risk of fatal stroke was reduced by 61%. (In absolute terms this actually amounted to 0.6%; NNT = 166)

About 24% of the subjects were not taking aspirin at baseline. Relatively few were taking statins.

The article does not mention if this subset of patients was started on these drugs. Certainly most of them should have received them. The benefit of ACE inhibitors is less in individuals receiving aspirin and statins for secondary prevention. If all patients had been taking aspirin, the results would have been even less clinically significant. We

should use all established (and lower cost) drugs and lifestyle measures to reduce risks before adding another high-cost drug with questionable effectiveness

If the NNT is calculated for benefit in one year instead of 4.5 Years, the NNT to prevent one stroke would be about 300.

My pharmacy quotes a price of $1.50 for one10 mg Ramipril (*Altace*).

Four and 1/2 years of therapy would cost over $2400.00. Is this benefit/harm-cost ratio compatible with a clinical benefit? Note that many were not taking prophylactic aspirin or statin drugs.

The article does not discuss adverse effects of ramipril.

In my opinion the benefit/harm-cost ratio is so low that adding ramipril is not clinically indicated. The paper is misleading. RTJ

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Again, Look Or "Spin"

3-13 CARDIOVASCULAR MORBIDITY AND MORTALITY IN LOSARTAN INTERVENTION FOR ENDPOINT REDUCTION IN HYPERTENSION STUDY (LIFE): A Randomized Trial Against Atenolol

Patients with hypertension, even when adequately treated, still have significantly higher rates of hypertension-related cardiovascular complications than matched people without hypertension. In patients with hypertension, beta-blockers and diuretics do not return rates of cardiovascular morbidity and death to normal. This might result from failure to achieve normal BP, or due to residual target damage such as left ventricular hypertrophy (**LVH**), or both.

LVH is a cardinal manifestation of preclinical cardiovascular disease and an independent risk factor for cardiovascular complications. Reversal of LVH has possible prognostic benefits. Blocking angiotensin II might be effective in reversing LVH.

"To date no drug for the treatment of essential hypertension has prevented cardiovascular morbidity and death beyond reductions in blood pressure achieved by beta-blockers and diuretics."

Losartan (*Cozaar*) is a selective angiotensin II receptor blocker. (Acts directly on the cell, not on the angiotensin-converting enzyme.)

This study aimed to establish whether losartan improves LVH beyond reducing BP, and if it reduced cardiovascular morbidity and death more than the beta-blocker atenolol (*Tenormin*; generic)

Conclusion: Losartan prevented more cardiovascular morbidity and death than atenolol for a similar reduction in BP.

STUDY

1. Double-blind randomized, parallel trial entered over 9000 participants age 55-80 (mean = 67).
2. All had hypertension (160-200/95-115; mean = 175/97)
3. All had LVH determined electrocardiographically. (Ie, patients were at high risk.)
4. Randomized to:

   A. Losartan 50 mg daily – increasing to 100 mg if needed to control BP, or

   B. Atenolol 50 mg daily – increasing to 100 mg if needed

Patients also received added hydrochlorothiazide (**HCTZ**) up to 25 mg daily (some also a third drug) trying to achieve a BP of less than 140/90.

5. Follow-up = 4.8 years.

RESULTS

1. Mean BP fell to a mean of 146/79 in the losartan group, and to 148/79 in the atenolol group.
2. To try to achieve target BP, the majority were increased to the 100 mg dose of both drugs, and had a third drug added.
3. Outcomes (4.8 years)

	Losartan	Atenolol	Difference	NNT 4.8 y
Primary composite endpoint (death, myocardial infarction, or stroke)	11 %	12.8%	1.8%	56
Death due to cardiovascular disease	4.4%	5.1%	0.7%	143
Stroke	5%	6.7%	1.7%	59
Myocardial infarction	4.3%	4.1%	-0.2%	500 (Harm)

5. Left ventricular hypertrophy decreased by about 5% in losartan group more than in the atenolol group.
6. Adverse effects were lower in the losartan group.

DISCUSSION

1. Losartan was more effective than atenolol in reducing frequency of composite endpoint of cardiovascular death, stroke, and myocardial infarction. (*Note that myocardial infarction was more common in the losartan group. RTJ*) Losartan was associated with a "significant" 13% reduction in the composite endpoint compared to the atenolol group. The reduction in death, and myocardial infarction was not significant. The difference was due to a "significant" reduction in stroke.
2. The mean BP in both groups was reduced by the same amount.
3. Losartan substantially reduced the rate of fatal and non-fatal stroke by 25%. [1]
4. The losartan group experienced a lower rate of adverse effects. [2]
5. "Our results are directly applicable to clinical practice and should affect future guidelines." [3]

CONCLUSION

The angiotensin II blocker losartan prevented more combined cardiovascular morbidity and death and stroke than the beta-blocker atenolol for a similar reduction in BP. "Losartan seems to confer benefits (*in relation to stroke*) beyond reduction in BP."

Lancet March 23, 2002; 359: 995-1003 Original investigation by the LIFE study group, first author Bjorn Dahlof, Sahlgrenska University Hospital, Gothenburg, Sweden. **www.thelancet.com**

A generally favorable editorial in this issue (pp 990-91) comments;

The difference in incidence of stroke is "highly significant". (*Ie, the relative risk reduction. RTJ*)

Angiotensin blocking drugs provide renal protection in patients with diabetes beyond the reduction in BP. The question is – Do they also provide cardioprotection beyond their BP-lowering effects? It is only when patients are at higher absolute cardiovascular risk that differences between drug classes are seen. Benefits were demonstrated only in reduction of stroke.

Comment:

1 Expressed in terms of misleading *relative* risk reduction of stroke (25%) instead of *absolute* reduction (1.7%). This benefits only one patient in 59 over a period of 5 years.

2 In figure 6 (p 1000) discontinuation due to drug-related adverse events was about 6% in the losartan group, and about 11% in the atenolol group. I would expect a high number of adverse effects from 100 mg atenolol.

3 I believe this is an overstatement. Undoubtedly ACE inhibitors and angiotensin II blockers are excellent and beneficial drugs, but not in this clinical context.

I do not believe the results of the study can or should be applied to primary care:

A. The benefit of losartan applied to only one person out of 59 over 5 years. This may be "highly significant" statistically, but hardly significant clinically.

B. Before introducing a new, more expensive drug therapy we should first obtain all benefits of older, established, less expensive drugs and changes in lifestyles. In this study this would include smoking control (no mention of this) , weight control (no mention) , statins (no mention despite cholesterol levels being elevated at study end), beta-blockers, and aspirin. Except for the beta-blocker, the trial included none of these preventive measures.

C. I believe a more meaningful approach would be to start with low-dose diuretics and beta-blockers and then add an angiotensin blocker if needed. Keeping doses of individual drugs relatively low and then adding another drug, if necessary to reach target, will reduce adverse effects more than increasing the dose of the original drug to maximum before adding another drug.

D. This study was essentially a losartan –HCTZ vs atenolol-HCTZ trial. Instead of a diuretic + beta blocker vs diuretic + angiotensin blocker study, it should be diuretic + beta-blocker + angiotensin blocker vs diuretic + beta-blocker. The question of effectiveness in treating high risk hypertensive patients should not ask if losartan is better than atenolol, but whether the combination of losartan, atenolol, and HCTZ confers greater effectiveness over atenolol + HCTZ. We should not neglect the remarkable benefits of beta-blockers in these high risk patients.

E. *Cozaar* costs $1.50 for each 50 mg capsule. Five years of 100 mg daily would cost about $5000. This greatly reduces the benefit/harm-cost benefit ratio of this therapy.

I usually abstract articles which likely lead to some clinical benefit in primary care. I took the time to abstract and critique this article because I believe its conclusions may mislead clinicians who do not have the time to judge the study in detail. Putting a favorable "spin" on conclusions of studies seems to be occurring more frequently. . RTJ

The Placebo Effect Is With Us Always

3-14 DECONSTRUCTING THE PLACEBO EFFECT: *The Meaning Response*

There is a renewed interest in the placebo effect — on its the reality, ethics, and place in medicine. One widely reported study concluded that placebos are powerless (*NEJM 2001; 344: 1594-602***)**

The authors of this article present a new perspective to what has been known as the "placebo effect". The most recent serious attempt to try logically to define the placebo effect failed utterly. One definition: "A placebo is a substance or procedure without specific activity for the condition being treated. The placebo effect is the therapeutic effect produced by a placebo." This makes no sense whatsoever. It flies in the face of the obvious. "The one thing of which we can be absolutely certain is that placebos do not cause placebo effects. Placebos are inert and don't cause anything." [1]

The editorialists suggest thinking about this issue in a new way. "Although placebos clearly cannot do anything themselves, *their meaning can*." They cite several studies describing effects of placebo. One study compared effects of inert red pills vs inert blue pills. The investigators asked medical students to participate in a study of two "new" drugs, one a stimulant, and one a tranquilizer. Each student was given either blue or red pills. The students responded that the red tablets acted as stimulants, and the blue as tranquilizers. Also that two tablets had more effect than one. These effects have been widely replicated.

Another study of patients with headache, compared aspirin labeled with a widely advertised brand name, and the same aspirin without a label. The branded tablets were more effective than the non-labeled aspirin. "Aspirin relieves headache, but so does the knowledge that the pills you take are 'good' ones."

The authors define the *meaning response* as the physiological or psychological effects of meaning in the origins or treatment of illness. Meaning responses elicited after use of an inert treatment can be called the "placebo effect" when they are desirable, and the "nocebo effect" when they are undesirable. Most elements of medicine *are* meaningful, even if practitioners do not intend them to be so. The physician's white coat, his manner, style, and language are meaningful and can affect outcomes.

Placebo "analgesics" can elicit the production of endogenous opiates. "Analgesia" elicited with an injection of saline solution can be reversed by the opiate antagonist naloxone. Acupuncture analgesia can be reversed by naloxone. "To say that a treatment such as acupuncture 'isn't better than placebo' does not mean that it does nothing." Surgery induces a profound meaning response.

Biology differs in different places, not because of genetics, but because of complex cultural webs of meaning. In diverse cultures, control groups vary in their response to inert pills.

Practitioners can benefit clinically by conceptualizing this issue in terms of meaning responses rather than the "placebo effect". Placebos are inert. For humans, meaning is everything that placebos are not -- richly alive and powerful. We know little about this power. One reason we are so ignorant is that, by focusing on placebos, we constantly have to address the moral and ethical issues of prescribing inert treatments -- of lying. One cannot avoid meaning while engaging humans. Eliciting the meaning response requires remarkably little effort. ("You will be fine, Mr. Smith.")

Annals Int Med March 19 2002; 136: 471-76 "Perspective" first author Daniel E Moerman, University of Michigan, Dearborn. **www.archinternmed.com**

Comment:

1 The authors went on to qualify this statement. Placebos (eg, lactose) do not cause anything pharmacologically or biochemically by themselves. But the editorialists go on to state, placebos can lead to powerful psychological and

even biological effects in some patients (eg, induction of endogenous opiates)

I remember an old study which went something like this:

In a controlled study, 1000 subjects were given “placebo”. Five hundred of them took the placebo religiously; 500 complied poorly. Outcomes in the first 500 were much better.

The individual response to care and suggestion is basic to a favorable placebo response. RTJ

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So Is The Nocebo Effect

3-15 NONSPECIFIC MEDICATION SIDE EFFECTS AND THE NOCEBO PHENOMENON

This article (based on a MEDLINE search) used the nocebo phenomenon to explore the occurrence of adverse, *nonspecific* effects in patients taking active medications and suggest ways in which clinicians can deal more effectively with them.

ADVERSE EFFECTS OF DRUGS, SPECIFIC AND NON-SPECIFIC:

Many adverse effects are *specific* (adverse actions of a drug other than the one for which the drug is being used). They result directly from the drug's pharmacological activity – direct toxicity or idiosyncrasy (eg, antibiotic diarrhea; drug rash).

Other adverse effects perceived by patients cannot be attributed to any specific pharmacological action or idiosyncrasy. These *non-specific* adverse effects distress patients, add to the burden of illness, and increase costs. They may lead to non-adherence, cause physicians to discontinue what is otherwise appropriate therapy, or prompt attempts to treat the effects with additional drugs. Only a small fraction of non-specific side effects of drugs are reported. This is due in part to uncertainty as to whether the symptoms are non-specific or caused by the drug..

The nocebo ("I will harm") phenomenon may help us understand *adverse non-specific* effects — bothersome symptoms and/or physiological changes that follow the administration of an inert, chemically inactive substance that the patient believes is an active drug. The term was coined to distinguish the noxious or distressing effects from the perceived beneficial effects of an inert, chemically inactive substance that the patient believes is an active drug. (So called “placebo” -- "I will please" effect) . The term “nocebo” can be used broadly to refer to all the distressing symptoms that accompany administration of an inert substance.

Large reservoirs of preexisting, ambiguous somatic symptoms are available for attribution to a newly instituted medication. The symptoms of the underlying disease for which the patient is being treated may be mistakenly ascribed to the medication. Symptoms may be the somatic components of emotion (anxiety or depression) or psychosocial distress. Patients may mistakenly ascribe symptoms of mild infirmities or benign, self-limited aliments (eg, headache, cramps, extrasystoles) to the medication. One study ascertained the incidence of 25 commonly reported symptoms in healthy persons who were not taking any medication. Many reported fatigue, difficulty concentrating, drowsiness, headache, and dizziness. Only 19% reported experiencing no symptoms in the previous 3

days.

"Thus when a patient starts taking a new medication, there is already a large reservoir of bodily symptoms available for misattribution by the patient to the medication."

The mechanisms underlying the nocebo effect are not clear. Conditioned learning and expectancy effects have been implicated. Patients who expect distressing side effects before taking a medication are more likely to develop them. One trial seeking informed consent specifically mentioned to some patients a possible adverse effect ("gastrointestinal irritation"). The possible adverse effect was not mentioned to others. Patients in the first group reported higher incidence of GI upset. Information given a patient about a drug's possible side effects modifies expectations of it and the response to it. Expectations induce symptoms in healthy non-patients. Many healthy volunteers experienced a headache after being told that a mild electric current that induces headache would be passed through their heads. (No current was administered).

Many patients may manifest adverse effects to a new drug because they have experienced adverse effects to other drugs in the past. "Patients can be conditioned to develop medication side effects."

Several psychological characteristics (anxiety, depression, somatization) have been associated with nocebo symptoms. "Depressed patients are somatically preoccupied, expect to suffer and experience discomfort, and don't feel they deserve to get better." Likelihood of discontinuing medication is high in this group.

Non-specific *beneficial* effects are assumed to occur in patients taking active drugs. This accounts for some fraction of the drug's total beneficial therapeutic effect. “Placebo” controls are important in drug trials to determine the true fraction of the overall treatment benefit attributable to the drug's specific, pharmacological activity. In controlled trials, a placebo control is a totally inert substance which the patients believe is an active drug. Any beneficial effect the patient attributes to the control substance is really not due to the inert substance, but due to the patient’s meaningful response to it. The true benefit of the active drug is considered to be the total benefit minus the placebo benefit. By analogy, some fraction of the adverse effects experienced by patients taking active drugs can be attributed to the nocebo effect. Approximately one quarter of patients taking a totally inert substance, believing it is an active drug, report adverse side effects.

The symbolic properties that a patient attributes to the medication reflect the information, opinions, and beliefs she has about it. This may be powerfully shaped by mass media, the internet, and direct advertising by drug companies.

CLINICAL IMPLICATIONS AND SUGGESTIONS FOR MANAGEMENT:

When a patient reports troublesome adverse effects, do not automatically assume they result from the pharmacological action of the drug and therefore necessitate dosage adjustment, discontinuation, or addition of another drug to treat the symptoms. (*A dangerous round-robin. RTJ*) Suspicion of a nocebo effect is heightened when the symptoms are vague, ambiguous, or prevalent in daily life, and when the patient has a history of negative side effects to other drugs.

Identify patients who somatize, are anxious, or depressed. They are at greater risk of nocebo effects. Ask the patient about being "especially sensitive" to drugs. and if they have had "bad experiences" to medication.

Use a 2-step, collaborative strategy for prescribing:

1. The goal of the first phase is simply to help the patient tolerate a very low dose of medication, Doses may be subtherapeutic. The objective is to allow the patient to get used to the idea of taking the drug. Because symptoms of the underlying medical condition are likely to persist during this phase, the patient may conclude

prematurely that the drug is ineffective. It is important to explain that a gradual titration may mean that symptoms will persist a while longer.

2. In the second phase, dose is gradually increased into the therapeutic range, acknowledging whatever side effects develop and coupling this with support and encouragement. Reassure the patient that, although non-specific side effects are bothersome, they are not medically dangerous.

If nonspecific adverse effects occur, provide an explanation, and help the patient re-attribute them. The goal is not to eliminate the adverse effects, but to help the patient tolerate them.

If adverse effects occur, find out if the patient is dissatisfied with her care. Patients may harbor misgivings, uneasiness, of suspicions about their treatment, but may feel uneasy about voicing concerns. Reporting troublesome side effects may be a less confrontational way of expressing such dissatisfaction. Again, the goal is not to eliminate the adverse effect, but to help patients tolerate them.

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Comment:

This is another good example of the uncertainties primary care clinicians encounter daily. There may be no good way to separate true adverse effects from nocebo effects in individual patients. Starting low and going slow may help some patients to greater tolerance. In fact, for some chronic conditions (hypertension, diabetes) starting below the PDR recommended initial dosage may be the best approach. (PDR often suggests initial doses which are above the individual's requirement for an adequate response.) Clinicians and patients may accept a partial response rather than increasing dosage to the point of adverse effects.

To clarify these concepts in my mind, I considered non-specific responses to drugs, and to totally inert substances to occur in several different circumstances:

1. Drug therapy: A beneficial effect can occur which has nothing to do with a drug's pharmacological action. This is usually termed the "placebo" effect of the drug. It is the patient's meaningful response to the drug.
2. Drug trials: Beneficial effects occur when an inert substance (always called the placebo) given in active drug vs placebo trials. Any beneficial effect from the inert substance represents the patient's meaningful response to it. (The "placebo" response.) The true pharmacological effect of the drug then equals the total beneficial effect obtained minus the "placebo" effect. Likewise, in placebo vs active drug trials, some patients will react adversely to the so-called placebo (the inert substance). Some of the reported adverse effects and withdrawals in the drug trial must be due to the "nocebo" effect. How do investigators determine how many?

Clinicians welcome non-specific beneficial effects and do not bother to explain them to patients. Non-specific adverse effects are bothersome and also difficult to explain. RTJ