

# **PRACTICAL POINTERS**

## **FOR PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

**APRIL 2005**

**THIAZIDE THE DRUG OF FIRST-CHOICE IN BLACKS WITH HYPERTENSION**

**HYPERTENSIVE END-STAGE RENAL DISEASE BEGINS WITH A BP OF 140/90**

**NEITHER ACE NOR CB SUPERIOR TO THIAZIDE IN PREVENTION OF KIDNEY DISEASE**

**MODIFIED MEDITERRANEAN DIET ASSOCIATED WITH LONGER SURVIVAL**

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**GENE DEFECT DISCOVERED IN PATIENTS WITH MACULAR DEGENERATION**

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## **HIGHLIGHTS AND EDITORIAL COMMENTS APRIL 2005**

*Thiazide the Drug of First-Choice for Blacks as Well as Whites.*

### **4-1 OUTCOMES IN HYPERTENSIVE BLACK AND NON-BLACK PATIENTS TREATED WITH CHLORTHALIDONE, AMLODIPINE, AND LISINOPRIL**

Blacks have the highest morbidity and mortality from hypertension of any population group in the USA.

The choice of the most effective and efficacious first-choice antihypertension drug is therefore important. This has been controversial in blacks.

This study asks if the benefits of thiazide diuretic therapy (chlorthalidone) compared with an ACE – inhibitor (lisinopril) and Calcium blocker (amlodipine) extended to black patients.

In blacks, neither the ACE nor the CB was more effective than the thiazide diuretic in preventing the primary outcome of fatal CVD + non-fatal-MI, or any other major cardiovascular or renal outcome.

Chlorthalidone was superior to ACE and CB in reducing incidence of heart failure.

Chlorthalidone was associated with a lower incidence of stroke than lisinopril.

Much of the comparative benefit may have been due to the greater reduction in systolic BP associated with chlorthalidone.

“Thiazide-type diuretics remain the drugs of choice for initial therapy of hypertension in both black and non-black hypertensive patients.”

*Using a diuretic as first-line therapy in both blacks and whites is associated with considerably lower costs over the years.*

*Costs; Chlorthalidone and hydrochlorothiazide cost 9 to 12 cents a day*

*Prinivil 53 cents a day ; Norvasc \$1.40 a day.*

**“Hypertensive End-Organ Damage Begins With A BP Below 140/90.”**

### **4-2 ELEVATED BLOOD PRESSURE AND RISK OF END-STAGE RENAL DISEASE IN SUBJECTS WITHOUT BASELINE KIDNEY DISEASE**

Establishing a detrimental effect of lesser degrees of BP elevation on the kidneys is difficult because kidney disease itself can elevate BP. This study asks: What is the importance of hypertension as a risk factor for ESRD?

A graded association between baseline BP and risk of ESRD existed among subjects without clinical evidence of kidney disease at baseline. Even relatively modest elevations of BP were associated with an increased risk of ESRD. “Hypertensive end-organ damage begins with a BP below 140/90.”

At any given level of BP there was a much higher risk of ESRD among blacks and patients with diabetes.

*Again demonstrating that risk of disease follows a linear pattern. There is no “normal” BP cut point.*

*Extra vigilance is required for black patients and for those with diabetes.*

## *Neither Amlodipine Nor Lisinopril Was Superior To Chlorthalidone*

### **4-3 RENAL OUTCOMES IN HIGH-RISK HYPERTENSIVE PATIENTS WITH AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR A CALCIUM CHANNEL BLOCKER VS DIURETIC**

This subset of the study assessed outcomes in the entire group ( n = 33 000) for renal outcomes. The methods used were identical to those in the study of blacks. Chlorthalidone, lisinopril, and amlodipine were used separately as first line therapy.

In both diabetic and non-diabetic participants, the 6-year rate of ESRD for those assigned to chlorthalidone was no different from those assigned to lisinopril. The benefits of ACE inhibitors (and angiotensin blockers) have been attributed to their effects on the renin-angiotensin system and their unique anti-proteinuric effects. Epidemiological studies have demonstrated a strong association between BP and ESRD outcomes. There was, however little difference in BP between the chlorthalidone and lisinopril groups.

*What is the message for primary care clinicians? Fortunately, we are not limited to an either-or choice of therapy as in the trial. Most high-risk hypertensive patients (with and without diabetes) will require two or three drugs to reduce BP as much as possible. A combination of a diuretic, an ACE, and a calcium blocker would be appropriate.. The diuretic should not be omitted. Addition of a beta-blocker should be considered in some patients.*

### ***Associated with longer survival.***

### **4-4 MODIFIED MEDITERRANEAN DIET AND SURVIVAL**

The Mediterranean diet (**MD**) is characterized by a high intake of vegetables, legumes, fruits, and cereals (largely unrefined); a moderate to high intake of fish; a low intake of saturated fats; a high intake of unsaturated fats (particularly olive oil); low to moderate dairy products; a low intake of meat; and a modest intake of ethanol, mostly as wine.

This study examined whether adherence to a modified MD (poly-unsaturated fats substituted for mono-unsaturates) was associated with longer life expectancy among elderly Europeans.

Means scores on the 10-point MD scale varied considerably between countries. Greece was highest (6.25); Spain next (5.61); Netherlands was lowest (2.92).

An increase in this modified MD score was associated with lower overall mortality. A two-unit increment corresponded to a reduction on 8% in mortality.

*I believe the modification (substituting poly-unsaturated fats for mono-unsaturated fat) is a clinically important point. Poly-fats are more accessible in our culture than mono-fats.*

### ***Too Often, Large Numbers Of Patients Are Being Treated Without Benefit.***

### **4-5 NUMBERS NEEDED TO TREAT (NEEDLESSLY?)**

The authors suggest a new index NNT(needlessly) to complement NNT(benefit). The higher the number, the greater the treatment burden.

For example, if the absolute difference between drug compared to placebo is 2% over 5 years, the NNT(benefit one patient) = 50. Of these, only one of 50 is benefited; 49 are treated (needlessly).

NNT(benefit) puts the emphasis on the positive side. But it tends to obscure the reality, that, too often, large numbers of patients are being treated without benefit.

The authors believe the new parameter will remind us that we should not be complacent about our inability to better identify patients who will benefit from our well-meaning interventions.

NNT(needlessly) may also help patients decide on their course of therapy.

*This is a good illustration of the uncertainty principle of therapeutics, which is related to all treatments. We cannot judge beforehand which patients will benefit and which ones will be treated unnecessarily. The numbers in the latter will almost always be higher than the former.*

*The number needed to harm [NNT(harm)] is another helpful index. It can be easily calculated from data presented in trials. Usually, the older a patient becomes the greater the NNT(harm).*

*We might also consider the “Money Needed to Treat” (MNT). (Ie, the cost of a drug to benefit one patient + the cost of treating many patients needlessly. See the following. RTJ*

### ***The Cost Of Treating Patients Who Benefit + Those Who Do Not Benefit.***

#### **4-6 “MONEY” NEEDED TO TREAT (MNT)**

The costs of treatment (money needed to treat to benefit one patient) can be easily calculated from analysis of trials which report the NNT(to benefit one patient over a given duration of therapy) in absolute terms. And by determining the cost of the drug.

A trial reported in NEJM April 7, 2005 “Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease” compared use of 80 mg the statin drug atorvastatin (*Lipitor*) with 10 mg. The LDL-cholesterol was lowered to a greater extent in the 80 mg group.

Over 5 years, major cardiac events occurred in 8.7% in the 80 mg group, and 10.9% in the 10 mg group Absolute difference = 2.2%; NNT(over 5 years to benefit one patient) = 45. Thus, 44 would be treated needlessly.

Based on the NNT (benefit) + the NNT(needlessly), the total cost of the 80 mg dose (44 + 1) = \$65 700

Conversely, patients may be told that they will spend \$1460 over 5 years to achieve a one in 45 chance of benefit.

### **“The Moral Basis of the Right to Die is the Right to Good Quality Life” “Mere Existence Is Not An Automatic Good.”**

#### **4-7 “RIGHT TO DIE”**

A general question is whether there such a thing as a right to die. The editorialist believes there is for the following reasons:

- 1) Every human rights convention recognizes a fundamental right to life.
- 2) Paradoxically, as it might at first seem, this also entails a right to die.

A. Life in the phrase “the right to life” does not mean bare existence. It means existence that has a certain minimum quality.

B. Mere existence is not an automatic good

“It is perhaps characteristic of humankind that it regards reasoned choices about when and how to die as morally problematic, whereas ignoring the question and hoping for the best is seen as acceptable or even right.”

Lawyers and doctors distinguish between withholding treatment with death as the result, and giving treatment that causes death. The first is considered permissible in law and ethics. The second is not. “But in fact, there is no difference between them.” Withholding treatment is an act, based on a decision, just as giving treatment is an act based on a decision. “Like the doctrine of double effect, which allows death-hastening levels of analgesia with the putative aim of controlling pain, the distinctions are fictitious. Death, after all, is the ultimate analgesic.”

*This one page commentary sums it up nicely*

### ***Primary Hyperparathyroidism Does Not Progress In Most Patients. “Most Have No Symptoms”***

#### **4-8 A 64-YEAR OLD WOMAN WITH PRIMARY HYPERPARATHYROIDISM**

This “Clinical Crossroads” conference presents the history of Mrs. Q, a 64-year old woman with mild hypercalcemia over 7 years. Her serum calcium has varied from time to time (10.1 to 11.3 mg/dL; normal = 9.0 – 10.5 mg/dL). Her parathyroid hormone level was 102 pg/mL (normal = 10 – 60 pg/mL); phosphate level = 3.4 mg/dL; albumin level = 4.1 g/dL

She was asymptomatic; never had any fracture or renal stone. No depression or mood swings. She did not take vitamin D or calcium. Her bone mineral density had decreased by 7% at the spine and by 5% at the femoral neck. 24 hour calcium excretion = 226 mg. Creatinine clearance normal.

A sestamibi scan revealed a localized increased uptake in the lower pole of the thyroid.

The consultant parathyroid surgeon concurred that the patient had mild chronic primary hyperparathyroidism.

How to proceed?

The article discusses epidemiology, pathophysiology, evaluation, end-organ effects, progression of the disease, effects on general well-being, surgical treatment, and recommendations of the National Institutes of Health for surgery.

*Our understanding of the natural history of primary hyperparathyroidism has been clarified and expanded over the years.*

*The article describes several points which were new to me:*

*Hyperparathyroidism in all its forms is characterized by a re-setting of the activity of the parathyroid glands to maintain a calcium level above normal range. A new balance is reached wherein the parathyroid hormone (PTH) excretion is increased to maintain the serum calcium at a higher than normal level. The higher calcium level restrains the gland and maintains its secretion at a higher set level. In all other forms of hypercalcemia PTH is suppressed.*

*Prospective studies over 10 years have reported that primary hyperparathyroidism does not progress in most patients. “The stability of most cases of primary hyperparathyroidism is surprising, considering the neoplastic nature of the disorder.” It may be related to the previously mentioned set-point for secretion of PTH. (Secretion of the adenoma is suppressed by the elevated serum calcium levels.) The adenoma may grow until the serum calcium set-point is reached. Then secretion of PTH secretion remains steady and the tumor stops growing.*

*A new approach, minimally invasive parathyroidectomy, requires preoperative localization of the adenoma by scanning with Technicium Tc99m-labeled sestamibi. If an adenoma is located, a limited incision may be made. Morbidity is lowered, operating time shortened, and hospital stay reduced.*

*If you practice primary care long enough you will unexpectedly encounter a patient with primary hyperparathyroidism. Most are identified by a chemical screen, which reveals high serum calcium.*

*I believe many primary care clinicians would inform this patient:*

- 1) The disease will not go away. It may progress and lead to increased bone loss over time.*
- 2) You have already undergone 7 years of testing, worry, inconvenience, and expense.*
- 3) Surgery will cure you and end all these concerns. The minimally invasive technique is safe.*

*Recovery is rapid.*

*Primary care clinicians choose your surgical consultant carefully.*

### ***Reduced Complications and Risk Of Death.***

## **4-9 THE EFFECT OF CARDIAC RESYNCHRONIZATION ON MORBIDITY AND MORTALITY IN HEART FAILURE**

Despite improvements in pharmacologic treatment, many patients with heart failure (HF) have severe and persistent symptoms. Their prognosis is poor. Such patients commonly have regions of delayed myocardial activation (left bundle branch block), leading to cardiac dyssynchrony.

Resynchronization was accomplished by a pacemaker containing 3 leads (right atrium, right ventricle, and left ventricle. This resulted in a reduction in intraventricular mechanical delay and end-systolic volume, and an increase in the left ventricular ejection volume. It improved symptoms and quality-of-life.

CR substantially reduced the risk of complications and deaths among patients with HF due to left ventricular systolic dysfunction and cardiac dyssynchrony. The benefits were in addition to those afforded by pharmacologic therapy. Over the study period, for every nine devices implanted, one death and 3 hospitalizations for major cardiovascular events were prevented. The reduction in risk of death is similar to that associated with beta-blocker therapy.

*Obviously not a panacea. Experienced consultants must be chosen with care. Patients should be aware of the high rate of complications, and the likelihood of improvement. The greatest benefit may be improving quality-of-life.*

*See illustration of lead placement on page 1595*

*Enables The Ventricles To Contract Simultaneously.*

#### **4-10 RESYNCHRONIZING VENTRICULAR CONTRACTION IN HEART FAILURE**

The biventricular-pacemaker implantation is technically demanding. It provides atrial-based, biventricular stimulation. Three leads are placed to pace 1) the right atrium, the 2) right ventricle, and the 3) left ventricle. The left ventricular lead is inserted into the coronary sinus (in the right atrium) and advanced into a cardiac vein on the lateral wall of the left ventricle. This enables the ventricles to contract simultaneously.

Complications of insertion are more frequent than for conventional pacemaker insertion

*See illustration of the placement of the pacemaker leads on page 1595.*

*Primary care clinicians should be able to advise this subset of patients if the procedure is available.*

*The Clinical Hallmark Is Fatigable Muscle Weakness Which Improves With Rest and Application Of Cold*

#### **4-11 DOES THIS PATIENT HAVE MYASTHENIA GRAVIS?**

This article reviews: anatomical and physiological origins of symptoms and signs; how to elicit symptoms and signs; anticholinesterase tests; and analysis of articles reviewed.

The approaches to diagnosis and treatment have evolved over the years. Testing now includes the ice pack test, the rest test, the sleep test, and the peek sign.

“Fluctuating weakness that worsens with exertion and improves with rest or with application of ice or cold is never normal.” The fluctuation is dramatic and occurs rapidly.

Bear in mind that the initial fluctuating weakness of MG may become fixed over time if severe enough.

Certain historical features (speech becoming unintelligible after prolonged periods) of signs (peek test) maybe useful in diagnosis. Their absence does not rule it out.

The ice test, sleep test, and response to anticholinesterase agents are useful in confirming the diagnosis. A positive test result should prompt proceeding with acetylcholine receptor antibody testing and specialist referral.

*The authors did not mention a common associated abnormality—enlargement of the thymus. This is frequent enough, I believe, to warrant imaging in suspected cases of MG.*

*The patient with MG, on first presentation, should present suggestive symptoms and signs. Speaking from personal experience, it is embarrassing to miss the diagnosis.*

**“Ask Your Doctor if X is Right for You”**

#### **4-12 DIRECT-TO-CONSUMER ADVERTISING**

##### ***A Haphazard Approach to Health Promotion***

DTCA drives sales of newer, more expensive products for symptomatic relief of chronic conditions. The market potential is huge. Erectile dysfunction, arthritis, and allergies are the most common conditions advertised.

“Relying on emotional appeals, most advertisements provide a minimal amount of health information, describe benefits in vague, qualitative terms, and rarely offer evidence of support claims.”



The great majority of physicians believe that DTCA does not provide balanced information. The FDA rarely writes regulatory letters. “Millions of patients are exposed to misleading advertisements.” Nearly 80% of physicians think that DTCA encourages patients to seek treatments they do not need. Less than 10% of physicians consider DTCA a positive trend in health care.

*Is ED a manufactured “disease”? Is drug treatment mainly recreational?*

*I confess that advertisements on TV touting a drug in market terms and then asking the listener to “Ask your doctor if the drug is right for you” irritates me. It would require considerable time and patience to educate individual patients about the benefit/harm-cost ratio of a given drug. It may be easier to submit as gracefully as possible.*

*I believe claims by drug companies that DTCA is for instruction and benefit of the consumer are specious. The purpose is to market the drug and increase profits.. After all, we live in a capitalistic society.*

***Associated With A Slight Reduction In Days Of Heavy Drinking.***

#### **4-13 EFFICACY AND TOLERABILITY OF LONG-ACTING INJECTABLE NALTREXONE FOR ALCOHOL DEPENDENCE**

The opioid antagonist naltrexone has been shown to be effective for treatment of alcohol dependence (AD). The FDA approved naltrexone in 1994 to treat AD after it was shown to reduce drinking frequency and likelihood of relapse to heavy drinking.

However, adherence to daily oral therapy is problematic, as it is with other medications.

Recently a new formulation of naltrexone has been made available. When given by injection, it releases the drug over a period of one month without daily peaks in concentration.

A randomized, double-blind, placebo-controlled multicenter trial followed over 400 patients (mean age = 45). All were considered to be AD and almost all were still actively drinking (median heavy drinking days per month = 20). All were seeking treatment for their AD.

Randomized to: 1) monthly injections of 380 mg long-acting naltrexone, or 2) placebo injections.

All also received low-intensity psychosocial intervention.

Follow-up = 6 months.

Conclusion: Long-acting naltrexone, given by injection once a month, was associated with a slight reduction in days of heavy drinking.

*Authors (with concurrence from journal editors) persist in reporting efficacy as percentages. (“Naltrexone resulted in a 25% reduction in the event rate of heavy drinking days”).*

*Results of the trial were not impressive. Dropout rate was high. Women did not benefit. Adverse effects were frequent. “Spin” was evident.*

*The most evident benefit shown by the study was in the “placebo” group (motivated patients who received counseling). At 6 months there was a median reduction in days of heavy drinking per month from about 19 to about 6. Naltrexone was associated with a further reduction from 6 to 3 days. (My assessment of the figure 2 page 1622). Over the 6 months, in the placebo group there was a median of 56 cumulative days of heavy drinking vs 47 cumulative days in the naltrexone group, a difference of only about 9 days.*

*Should primary care clinicians administer long-acting naltrexone by injection? I believe only in exceptional circumstances. If a patient with AD approaches the primary care clinician for help, the desire to quit must be understood to be strongly motivated. The clinician must be able to provide adequate counseling. Follow-up must be rigid. The clinician and patient must enter a contract to guide compliance. The small added benefit from naltrexone must be made clear.*

*We await better treatments, perhaps with the addition of two or more pharmacological agents (eg, acamprosate).*

*The study was sponsored by Alkermes and Pharmacological Product Development Inc. who collected and monitored the data. Data were managed and analyzed by Alkermes clinical and statistical staff.*

***“May Lead To Treatment Which Slows Disease Progress”***

#### **4-14 GENE DISCOVERY PROVIDES CLUES TO CAUSE OF AGE-RELATED MACULAR DEGENERATION**

A gene variant may be responsible for about half of the 15 million cases of AMD in the US. Using techniques from the Human Genome Project, investigators have identified a common variant of the complement factor H (CFH) gene that explains about 50% of cases:

Individual who possess a certain variant of the CFH gene are at increased risk of AMD. The protein [tyrosine replaced by histidine] encoded by the variant fails to bind to receptors on cells on the retina and surrounding blood vessels. The protective effect of normal CFH is lost. This leads to increased inflammation in the retina and choroid.

Discovery of this variant may lead to treatment which slows disease progress. A modest slow-down would be sufficient to preserve a patient’s vision for the rest of his life.

*While not a practical point at this time, I felt the “News” was provocative enough to abstract.*

## ABSTRACTS APRIL 2005

### *Thiazide The Drug Of First-Choice For Blacks as Well as Whites.*

#### **4-1 OUTCOMES IN HYPERTENSIVE BLACK AND NON-BLACK PATIENTS TREATED WITH CHLORTHALIDONE, AMLODIPINE, AND LISINOPRIL**

Blacks have the highest morbidity and mortality from hypertension of any population group in the USA. Mortality from end-stage renal disease, coronary heart disease (**CHD**), heart failure (**HF**), and stroke is higher than in the white population.

The choice of the most effective and efficacious first-choice antihypertension drug is therefore important. This has been controversial in blacks.

The ALLHAT trial <sup>1</sup> (over 42 000 high risk black and white hypertensive subjects) determined that a regimen based on a thiazide-type diuretic was just as effective in preventing CHD as regimens based on an alpha-blocker, an ACE inhibitor (**ACE**), or a calcium blocker (**CB**). Overall, in the entire cohort of subjects, the thiazide was more effective than the other agents in preventing heart failure, and more effective than the alpha-blocker and the ACE inhibitor in preventing stroke and a composite of cardiovascular disease outcomes.

This study asks if the benefits of diuretic therapy (compared with ACE and CB) extended to black patients.

Conclusion: As initial therapy, diuretic was just as beneficial as ACE and CB, and in some respects superior. Thiazides remain the drug of first choice for initial therapy for blacks as well as whites.

#### STUDY

1. Followed a prespecified subset of over 11 000 black patients in the ALLHAT study.
2. All had a history of hypertension; mean BP = 146/85. (Most were already receiving treatment)
3. All were over age 55 and had at least one other risk factor for CVD. (A high-risk group)
4. Randomized to regimens based on: 1) a calcium blocker (amlodipine; *Norvasc*; *Lortrel*) ;  
2) an ACE inhibitor (lisinopril; *Prinivil*; *Zestril*; *generic* ), or 3) a thiazide (chlorthalidone; *generic*)
5. Other drugs (eg, a beta-blocker or an alpha blocker) could be added to achieve a goal BP less than 140/90.

The protocol prohibited any of the 3 study drugs from being used at the same time as either of the other 2.

6. Primary outcome = combined fatal CHD or non-fatal myocardial infarction (**MI**).
7. Secondary outcomes included all-cause mortality, stroke, combined cardiovascular disease, and end-stage renal disease.
8. Follow-up = up to 6 years.

#### RESULTS

1. At baseline, blacks were more likely than whites to be women, have diabetes, smoke cigarettes, and have ECG evidence of left ventricular hypertrophy.
2. Outcomes over 6 years:

- A. Combined fatal CHD + nonfatal MI; no significant difference between the 3 drugs.
  - B. Blood pressure: Chlorthalidone was associated with a slightly lower systolic BP than the other 2 drugs. At 4 years more blacks taking chlorthalidone reached the cut point of BP under 140/90.
  - C. Stroke: Chlorthalidone treatment was associated with a significantly lower incidence of stroke when compared with lisinopril. (RR = 1.4)
  - D. Heart failure: Chlorthalidone was associated with a significantly lower incidence of HF than either lisinopril or amlodipine.
  - F. End stage renal disease: No difference between groups.
  - G. All-cause mortality: No difference between groups.
2. Adverse effects: Chlorthalidone was associated with a greater incidence of lowering of serum potassium (< 3.5 MEq/L). and slightly higher fasting glucose levels. ACE was associated with a higher incidence of angioedema.
  3. Serious adverse effects were rare in all 3 groups.

## DISCUSSION

1. The findings by race mostly parallel those in the entire cohort of the ALLHAT trial (where 2/3 of the subjects were white). Neither ACE nor the CB was more effective than the thiazide diuretic in preventing the primary outcome of fatal CVD + non-fatal-MI, or any other major cardiovascular or renal outcome.
2. Chlorthalidone was superior to ACE (lisinopril) and CB (amlodipine) in reducing incidence of heart failure.
3. Chlorthalidone was associated with a lower incidence of stroke than lisinopril.
4. Much of the comparative benefit may have been due to the greater reduction in systolic BP associated with chlorthalidone.
5. A high % of subjects required 2 or more antihypertension drugs. Since ACE, CB, and thiazide were being compared in the trial as first-line agents, and by protocol, could not be used in combination, the most commonly added 2<sup>nd</sup> drug was the beta-blocker atenolol. Clonidine (alpha blocker) was next.
6. Thiazide-type diuretics are indicated as the drug of choice for initial treatment of high BP in both blacks and whites.
7. What is the second or third (add-on) choice? *(Clinically, we are not limited to using the 3 drugs simultaneously. Choice would depend on response of BP and concomitant abnormalities. I believe a beta-blocker should be considered based on cost and safety. In the trial it was the most used add-on. RTJ)*

## CONCLUSION

For blacks, thiazide diuretic therapy based on chlorthalidone as first-line therapy was equally as effective as an ACE and a CB for any prespecified outcome. Thiazide diuretic therapy resulted in the lowest risk of heart failure and a lower risk of stroke (compared with ACE).

“Thiazide-type diuretics remain the drugs of choice for initial therapy of hypertension in both black and non-black hypertensive patients.”

JAMA April 6, 2005; 293: 1595-1608 Original investigation by the “Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial” (ALLHAT) Collaborative Research Group, first author Jackson Wright Jr. Case Western Reserve University, Cleveland, Ohio.

1 JAMA 2002; 288: 2981-97 *See Practical Pointers December 2002 [1-12]*

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**“Hypertensive End-Organ Damage Begins With A BP Below 140/90.”**

#### **4-2 ELEVATED BLOOD PRESSURE AND RISK OF END-STAGE RENAL DISEASE IN SUBJECTS WITHOUT BASELINE KIDNEY DISEASE**

Many cases of end-stage renal disease (**ESRD**) are ascribed to hypertension. But, because renal disease itself can cause hypertension, is the hypertension seen in patients with ESRD due to the underlying renal disease? Or does hypertension contribute to the renal disease?

This study asks: What is the importance of hypertension as a risk factor for ESRD?

Conclusion: Even modest elevations of BP are an independent risk factor for ESRD.

#### **STUDY**

1. Considered a large cohort (over 316 000) adult members of the Kaiser Permanente health care delivery system. All received Multiphasic Health Checkups between 1964 and 1985. Mean age at baseline = 37
2. All had estimated glomerular filtration rates of 60 mL/min per 1.73 m<sup>2</sup> or higher. All had negative urine dipsticks for proteinuria and hematuria. None were considered to have renal disease.
3. The cohort was divided into 7 BP levels.
4. Determined incidence of ESRD over 8 210 000 person-years of follow-up.

#### **RESULTS**

1. During follow-up, 1149 cases of ESRD occurred.
2. There was a strong, graded relationship between BP and risk of ESRD.
3. Overall, the relationship between BP and ESRD persisted after adjustment for multiple other factors.

	Adjusted relative risk of ESRD
1) Optimal; <120.80	1.00
2) Normal, not optimal; 120-129/80-84	1.60
3) High normal; 130-139/85-89	2.00
4) Stage 1 hypertension; 140-159/90-99	2.60
5) Stage 2 hypertension; 160-179/100-109	3.80
6) Stage 3 hypertension; 180-209/110-119	3.90
7) Stage 4 hypertension; 210/120 and higher	4.20

4. The age-adjusted associations between BP and ESRD were much higher in blacks vs white and among diabetics.

## DISCUSSION

1. There are few studies to support the widely held belief that non-malignant hypertension is an important cause of ESRD. Establishing a detrimental effect of lesser degrees of BP elevation on the kidneys is difficult because kidney disease itself can elevate BP.
3. This study demonstrated a graded association between baseline BP and risk of ESRD existed among subjects without clinical evidence of kidney disease at baseline. Even relatively modest elevations of BP were associated with an increased risk of ESRD. “Hypertensive end-organ damage begins with a BP below 140/90.”
4. At any given level of BP there was a much higher risk of ESRD among blacks and patients with diabetes. .

## CONCLUSION

Non-malignant hypertension is an independent risk factor for ESRD in patients without baseline kidney disease. Risk is increased even with relatively modest elevations of BP.

Archives Int Med April 25, 2005; 165: 923-28 Original investigation, first author Chi-yuan Hsu, University of California, San Francisco.

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### *Neither Amlodipine Nor Lisinopril Was Superior To Chlorthalidone*

#### **4-3 RENAL OUTCOMES IN HIGH-RISK HYPERTENSIVE PATIENTS WITH AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR OR A CALCIUM CHANNEL BLOCKER VS DIURETIC**

This post hoc analysis is a companion to the preceding article. It is a report from the ALLHAT group and many of the same investigators.

This subset of the study assessed outcomes in the entire group ( n = 33 000) for renal outcomes. The methods used were identical to those in the study of blacks. Chlorthalidone, lisinopril, and amlodipine were used separately as first line therapy. A beta-blocker and an alpha-blocker could be used as add-on therapy to reduce BP. (The protocol specified that none of the 3 primary drugs could be used together.)

At baseline the study divided the entire group of patients into 3 groups according to: 1) a normal GFR; 2) mild decrease in GFR; and 3) moderate or severe decrease in GFR. Then compared renal outcomes (development of end-stage renal disease of and/or a decrement of 50% or more in glomerular filtration rate; **GFR**) over 5 years in patients taking the three different drugs.

## RESULTS

1. Over 5 years 448 patients developed ESRD.

2. Chlorthalidone vs amlodipine: No significant differences in incidence of ESRD in any of the three GFR groups. No significant difference in combined ESRD + 50% decline in GFR.
3. Chlorthalidone vs lisinorpil: No significant difference in incidence of ESRD in any of the three GFR groups. No significant difference in combined ESRD + 50% decline in GFR.
4. The 5-year rate of ESRD in diabetic patients was about twice that of non-diabetics.

## DISCUSSION

1. This study pre-specified renal outcomes as a secondary outcome. The large number of participants with reduced GFRs and diabetes allowed a head-to-head comparison of the effects of 3 drugs on renal disease outcomes.
2. In participants with reduced renal function, neither amlodipine nor lisinorpil was superior to chlorthalidone in lowering the incidence of ESRD or a composite of ESRD + a 50% or greater decline in GFR.
3. Regardless of whether hypertension is the cause or the consequence of kidney disease, when the two present together, high BP is associated with rapid progression, and adequate treatment of hypertension slows progression of the kidney disease and reduces the risk of ESRD. Thus there has been great interest in whether the choice of antihypertension drugs has an impact on renal disease progression.
4. Comparing diuretic with ACE inhibitor:  
In both diabetic and non-diabetic participants, the 6-year rate of ESRD for those assigned to chlorthalidone was no different from those assigned to lisinorpil, The benefits of ACE inhibitors (and angiotensin blockers) have been attributed to their effects on the renin-angiotensin system and their unique anti-proteinuric effects. Epidemiological studies have demonstrated a strong association between BP and ESRD outcomes. There was, however little difference in BP between the chlorthalidone and lisinorpil groups in this study.
5. “Our findings have particular relevance for the treatment of patients with established diabetic nephropathy.” Inhibitors of the renin-angiotensin system have been shown to be superior to conventional treatment in patients with diabetes. Guidelines recommend use of ACE inhibitors (and angiotensin blockers) as first-line treatment of diabetic nephropathy. But, the ALLHAT study showed no difference in outcomes between diuretic and ACE at any level of GFR. However, ALLHAT study did not specifically study patients with diabetic nephropathy and proteinuria. Thus, the study does not refute current recommendations for treatment. <sup>1</sup>

## CONCLUSION

In hypertensive patients with reduced GFR, neither amlodipine nor lisinorpil was superior to chlorthalidone in reducing the rate of development of ESRD or a 50% or greater reduction in GFR.

Archives Int Med April 25, 2005; 165: 936-46 Original investigation for the ALLHAT Research Group, first author Mahboob Rahman, Case Western Reserve University, Cleveland Ohio

**1** *Note the authors hedge in recommending diuretics over ACE in diabetics.*

*The diet was associated with longer survival.*

#### **4-4 MODIFIED MEDITERRANEAN DIET AND SURVIVAL**

The Mediterranean diet (**MD**) is characterized by a high intake of vegetables, legumes, fruits, and cereals (largely unrefined); a moderate to high intake of fish; a low intake of saturated fats; and a high intake of unsaturated fats (particularly olive oil); low to moderate dairy products; a low intake of meat; and a modest intake of ethanol, mostly as wine. The MD is associated with benefits to health. Variants of the diet have improved prognosis in patients with coronary heart disease.

This study examined whether adherence to a modified MD (poly-unsaturated fats substituted for mono-unsaturates) was associated with longer life expectancy among elderly Europeans.

Conclusion: The modified MD was associated with longer survival.

#### **STUDY**

1. Multicenter prospective cohort study (9 European countries) followed over 74 000 men and women over age 60. None had a history of coronary heart disease, stroke, or cancer. All were apparently healthy.
2. Obtained complete information about dietary intake by food frequency questionnaires..
3. Measured extent of adherence to the MD on a 10-point scale. Because of the lack of intake of olive oil in this cohort, the modification to the traditional MD consisted of a substitution of the sum of mono- + poly-unsaturated fats for mono-unsaturated fats.
4. Determined death from any cause.
5. Follow-up for about 170 000 person-years.

#### **RESULTS**

1. Means scores on the 10-point MD scale varied considerably between countries. Greece was highest (6.25); Spain next (5.61); Netherlands was lowest (2.92).
2. An increase in this modified MD score was associated with lower overall mortality. A two unit increment corresponded to a reduction on 8% in mortality.
3. When dietary exposures were calibrated across countries, the reduction in mortality varied from 1% to 12%. Benefit on mortality was strongest in Greece.

#### **DISCUSSION**

1. A higher dietary score that assessed adherence to a modified MD was associated with a significantly longer life expectancy in apparently healthy elderly people in 9 European countries.
2. The score was modified to include poly-unsaturated fats. Polyunsaturates are the principal unsaturated fats in diets in non-Mediterranean countries. They are an acceptable substitute when mono-unsaturates are not readily available.
3. The principal characteristic of the modified MD is its reliance on plant foods and unsaturated lipids. “The important point is that a diet that can be operationalized does have a relationship with mortality, and realistically achievable changes in diet are associated with a reduction in total mortality.”



## CONCLUSION

The MD, modified so as to apply across Europe, was associated with increased survival among older people.

BMJ April 30, 2005; 330: 991-95 Original investigation by **the** EPIC-Elderly Prospective Study Group reported by Antonia Trichopoulou, University of Athens Medical School, Athens, Greece.

A companion study by the same group appeared in Archives Int Med April 25, 2005—"Mediterranean Diet and Survival among Patients with Coronary Heart Disease in Greece". Adherence to the MD in cohort of persons with diagnosed coronary heart disease at enrollment was followed for an average of 4 years. Higher adherence by 2 units was associated with a 27% lower total mortality rate. The reduced mortality was slightly greater (31%) when deaths due to coronary disease were considered.

Diet should be considered an important therapeutic measure as well as a preventive measure.

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***Too Often, Large Numbers Of Patients Are Being Treated Without Benefit.***

### **4-5 NUMBERS NEEDED TO TREAT (NEEDLESSLY?)**

The number needed to treat (NNT) over a given time to benefit one person is a standard expression of evidence-based medicine. It is the reciprocal of the absolute difference between treatment groups (study drug vs placebo, or vs a second drug).

Trials report that the NNT to prevent on death in patients with a myocardial infarction with systemic nitrates is about 250. Thus the NNT needlessly = 249. The NNT (over 2 years) to benefit one patient with beta-blocker therapy for 2 years after a myocardial infarction is about 33. The NNT needlessly = 32.

The NNT (to benefit one patient) in the first instance is regarded as too high to recommend generalized clinical use. The NNT (benefit) in the second instance is the basis for a firm endorsement.

NNT(benefit) puts the emphasis on the positive side. But it tends to obscure the reality, that, too often, large numbers of patients are being treated without benefit.

The authors suggest a new index NNT(needlessly) to complement NNT(benefit). The higher the number, the greater the treatment burden.

The index could also be rendered as a percentage. If the NNT(needlessly) with nitrates is 250, 99.6% (249/250) would be treated without benefit. For treatment with beta-blockers the NNT(needlessly) would be 97%.

The authors believe the new parameter will remind us that we should not be complacent about our inability to better identify patients who will benefit from our well-meaning interventions.

NNT(needlessly) may also help patients decide on their course of therapy.

Lancet April 9, 2005; 365: 1307-08 Correspondence to Lancet first author Peter Bogaty Quebec Heart Institute,/Laval Hospital, Quebec, Canada.

*We might also consider the overall cost of treatment—"The Money Needed to Treat". (MNT) See the following.*

***The Cost Of Treating Patients Who Benefit + Those Who Do Not Benefit.***

**4-6 “MONEY” NEEDED TO TREAT (MNT)**

Based on the preceding article, which calls attention to a new parameter, the number to treat needlessly [NNT(needlessly)], large numbers of patients will be treated without benefit (and undoubtedly with some harm) to benefit one patient. (The benefit/harm-cost ratio may be low.)

The costs of treatment (money needed to treat to benefit one patient) can be easily calculated from analysis of trials which report the NNT(to benefit one patient over a given duration of therapy) in absolute terms. And by determining the cost of the drug.

A trial reported in NEJM April 7, 2005 “Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease” compared use of 80 mg the statin drug atorvastatin (*Lipitor*) with 10 mg. The LDL-cholesterol was lowered to a greater extent in the 80 mg group.

Over 5 years, major cardiac events occurred in 8.7% in the 80 mg group, and 10.9% in the 10 mg group. Absolute difference = 2.2%; NNT(over 5 years to benefit one patient) = 45. Thus, 44 would be treated needlessly.

Cost of the drugs:

Lipitor 80 mg = \$3.06 each

10 mg = \$2.26 each.

Difference = \$0.80

The extra cost of treating one patient for 5 years = \$1460

The total cost--“Money” needed to treat ; MNT(to benefit one patient over 5 years)

= \$1460 X 45 = \$65 700

Conversely, patients may be told that they will spend \$1460 over 5 years to achieve a one in 45 chance of benefit.

They may also be told that reported harm (elevation of liver enzymes) was 1% [NNT (harm) = 100] at least one chance in 100 they will be harmed

Each individual must choose based on his or her own assessment of the benefit/harm-cost ratio.

April 2005, Commentary by Editor of Practical Pointers.

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**“The Moral Basis of the Right to Die is the Right to Good Quality Life” “Mere Existence Is Not an Automatic Good.”**

**4-7 “RIGHT TO DIE”**

The question of the right to die has become one of the most important in contemporary ethics. The case of Terri Schiavo (vegetative state for years) in Florida has stimulated debate.

The question has two different aspects;

1) The assertion by individuals of their own right to die (eg, a living will).

- 2) For those not able express a wish to die, the request is made either by relatives (who believe that this would be the wish of the patient), or by medical practitioners (who judge that it is not in the patient's interest to be maintained on life support when there is no realistic chance of recovery).

The first is relatively simple. Individuals of sound mind and settled purpose who wish to die are, in many countries, free to commit suicide in the sense that, if the attempt fails, they will not be prosecuted for having tried. In most jurisdictions, people can refuse medical treatment even if the probable outcome is death. Problems arise when individuals seek medical help to die. In some jurisdictions (including Oregon) it is legal for a person to be given medical help to die in circumstances detailed in relevant covering laws.

The second aspect is also relatively straightforward when relatives and medical practitioners agree that withdrawing life support is appropriate. Problems arise when such consensus is lacking.

Underlying both aspects is the general question of whether such a thing as a right to die exists beyond the mere permission to die by suicide. The editorialist believes there is for the following reasons:

- 1) Every human rights convention recognizes a fundamental right to life.
- 2) Paradoxically, as it might at first seem, this also entails a right to die.

A. Life in the phrase "the right to life" does not mean bare existence. It means existence that has a certain minimum quality. The "minimum" is quite rich, giving its possessors access to a range of basic human goods such as relationships in which they are free as reasonably possible from distress and pain.

B. The idea that the right to life is a right to life of a certain minimum quality implies that mere existence is not an automatic good. When individuals maturely judge that their quality of life is below the minimum, they have a right to die if they have a settled and reasoned wish to do so. "Considerations of humanity then further imply that they have a supplementary right to assistance of the kind medical science can provide in dying painlessly and easily."

C. Other rights regarded as fundamental have their part here too: rights to privacy; freedom of thought; and personal autonomy, which together leave life's great questions to individual choice. The question of when and how to die is one of these questions, even though most persons leave the answer to chance. "It is perhaps characteristic of humankind that it regards reasoned choices about when and how to die as morally problematic, whereas ignoring the question and hoping for the best is seen as acceptable or even right."

D. Lawyers and doctors distinguish between withholding treatment with death as the result, and giving treatment that causes death. The first is considered permissible in law and ethics. The second is not. "But in fact, there is no difference between them." Withholding treatment is an act, based on a decision, just as giving treatment is an act based on a decision. "Like the doctrine of double effect, which allows death-hastening levels of analgesia with the putative aim of controlling pain, the distinctions are fictitious. Death, after all, is the ultimate analgesic."

In some cases the right to die is exercised on someone's behalf by third parties. When the third parties disagree, the question widens to include the rights of those related to, and responsible for the patient. Society automatically has an interest. Political and religious sentiments may obscure the interests of the patient in such cases. A dispassionate assessment of the facts in a court of law is the best way to reach a conclusion.

BMJ April 9, 2005; 330: 799 Commentary by A C Grayling, School of Philosophy, Birkbeck College, London, UK

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***Primary Hyperparathyroidism Does Not Progress In Most Patients. "Most Have No Symptoms"***

**4-8 A 64-YEAR OLD WOMAN WITH PRIMARY HYPERPARATHYROIDISM**

This "Clinical Crossroads" conference presents the history of Mrs. Q, a 64-year old woman with mild hypercalcemia over 7 years. Her serum calcium has varied from time to time (10.1 to 11.3 mg/dL; normal = 9.0 – 10.5 mg/dL). Her parathyroid hormone level was 102 pg/mL (normal = 10 – 60 pg/mL); phosphate level = 3.4 mg/dL; albumin level = 4.1 g/dL

She was asymptomatic; never had any fracture or renal stone. No depression or mood swings. She did not take vitamin D or calcium. Her bone mineral density had decreased by 7% at the spine and by 5% at the femoral neck. 24 hour calcium excretion = 226 mg. Creatinine clearance normal.

A sestamibi scan revealed a localized increased uptake in the lower pole of the thyroid.

The consultant parathyroid surgeon concurred that the patient had mild chronic primary hyperparathyroidism.

She would like to avoid surgery if possible. How to proceed?

*Epidemiology and pathophysiology:*

The patient presents a typical picture of primary hyperparathyroidism as seen in the US. It is judged to have a prevalence of about 1 in 1000, highest in postmenopausal women. A relatively few (under 10%) present with renal stones. Most have no symptoms.

Hyperparathyroidism in all its forms is characterized by a re-setting of the activity of the parathyroid glands to maintain a calcium level above normal range. A new balance is reached wherein the parathyroid hormone (**PTH**) excretion is increased to maintain the serum calcium at a higher than normal level. The higher calcium level restrains the gland and maintains its secretion at a higher set level. In all other forms of hypercalcemia, PTH is suppressed.

Parathyroid hormone acts to raise serum calcium by actions on 1) the gut (increased absorption), 2) the bone (resorption), and 3) the kidney (enhanced renal reabsorption).

*Evaluation:*

The patient undoubtedly has hyperparathyroidism. She has an inappropriately elevated level of parathyroid hormone in the presence of hypercalcemia. Hyperparathyroidism is the only condition in which this occurs.

Measurements of calcium, phosphate, creatinine, and PTH are necessary to make the diagnosis of primary hyperthyroidism. Serum 25-hydroxyvitamin D should also be measured to exclude vitamin deficiency. In the deficient state, absorption of calcium from the gut is impaired, serum calcium levels decrease and hyperparathyroidism may be exacerbated.

There is as yet, no accepted medical treatment. The disease can be cured by surgery, but, it is not clear whether every patient requires surgery. To make a recommendation for surgery vs observation we must ask: 1) What are the end-organ effects? 2) Is it likely to progress? 3) What are the risks of surgery? 4) Does surgery improve the general well-being?

*End-organ effects:*

Classical osteitis fibrosa cystica is rarely seen in the US. Osteoporosis is common. Cortical bone (eg, the forearm) is lost preferentially. Trabecular bone (eg, lumbar spine) is relatively preserved despite rates of bone turnover several times normal.

Occasionally nephrocalcinosis and progressive renal insufficiency occurs. Check for stone by abdominal X-ray.

Check serum creatinine, alkaline phosphatase, urinary calcium, and BMD to identify end-organ effects.

*Progression of the disease:*

Prospective studies have reported that primary hyperparathyroidism does not progress in most patients over 10 years. Serum calcium and PTH usually remain stable, and creatinine and BMD do not change. However, some do indeed have substantial increases in hypercalcemia, hypercalciuria, and declines in BMD. It is not clear if the presenting patient had progression.

“The stability of most cases of primary hyperparathyroidism is surprising, considering the neoplastic nature of the disorder.” It may be related to the previously mentioned set-point for secretion of PTH. (Secretion of the adenoma is suppressed by the elevated serum calcium levels.) The adenoma may grow until the serum calcium set-point is reached. Then secretion of PTH secretion remains steady and the tumor stops growing.

Interestingly, bisphosphonates may be harmful in these patients because they reduce serum calcium by inhibiting bone resorption. This may lead to increased growth of the adenoma and increased secretion of PTH.

*Surgical treatment:*

A new approach, minimally invasive parathyroidectomy, requires preoperative localization of the adenoma by scanning with Technicium Tc99m. If an adenoma is located, a limited incision may be made. Morbidity is lowered, operating time shortened, and hospital stay reduced. Rapid intraoperative assay of PTH can be used to confirm that resection of the adenoma has removed the source of the PTH.

Surgery may reduce incidence of renal stones and improve bone mineral density. Non-specific symptoms may improve. (This is debatable. Many patients do not note any change.)

*General well-being:*

Fatigue, weakness, depression, and memory problems are common complaints. It is difficult to ascertain if these non-specific symptoms are due to the disease. Some studies have reported post-surgical improvement.

*Recommendations of 2002 National Institutes of Health:*

Surgery is recommended when:

Serum calcium is 1 mg/dL or more above upper normal limit.

Urinary calcium excretion is over 400 mg daily

Impaired renal function (creatinine clearance reduced by 30% for age-matched controls).

BMD T-score less than -2.5 (matching the WHO Health Organization definition of osteoporosis)

Age younger than 50.

*Recommendations for Mrs. Q:*

She has asymptomatic hyperparathyroidism. According to the above recommendations, she does not have an indication for surgery. The consultant is concerned that her serum calcium levels may be increasing, and her BMD declining. Since the patient resists surgery, and because the data about progression are inconclusive, he recommends a 1 to 2 year follow-up to permit the patient to gain confidence about surgery, Follow-up requires repeated determinations of calcium, creatinine, and BMD.

JAMA April 13, 2005; 293: 1772-79 Discussant Gordon J. Strewler, Beth-Israel Deaconess Medical Center, Boston, Mass

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***Reduced Complications and Risk Of Death.***

**4-9 THE EFFECT OF CARDIAC RESYNCHRONIZATION ON MORBIDITY AND MORTALITY IN HEART FAILURE**

Despite improvements in pharmacologic treatment, many patients with heart failure (**HF**) have severe and persistent symptoms. Their prognosis is poor. Such patients commonly have regions of delayed myocardial activation (left bundle branch block), leading to cardiac dyssynchrony.

Restoring cardiac synchrony with properly placed pacemakers can improve ventricular function, symptoms, exercise capacity, and quality-of-life.

This study evaluated the effect of cardiac resynchronization (**CR**) on morbidity and mortality.

Conclusion: In patients with HF and cardiac dyssynchrony, CR reduced complications and risk of death.

**STUDY**

1. A multicenter, international trial randomized over 800 patients (median age = 66). All had left ventricular dysfunction, cardiac dyssynchrony, and symptomatic HF (NYHA class III or IV). All had received standard pharmacological treatment and remained in HF.
2. Left ventricular ejection fraction was no more than 35% (median = 25%); left ventricular end-diastolic

volume was increased; ORS interval 120 msec or more on the EKG (median = 160 msec). All also had an aortic pre-ejection delay of more than 140 msec, and an intraventricular mechanical delay of more than 40 msec, or delayed activation of the posterolateral left ventricular wall.

3. All subjects were in sinus rhythm. Patients with atrial arrhythmias were excluded (The authors state such patients cannot benefit from the atrial component of resynchronization.)
4. Randomized to: 1) cardiac resynchronization with a properly placed pacemaker (without a defibrillator) plus continued medical therapy, or 2) continued medical therapy alone.
5. Primary end-point = composite of death from any cause, or unplanned hospitalization for a major cardiovascular event (worsening HF, myocardial infarction, unstable angina, arrhythmia, stroke, and others). Follow-up = 29 months.

## RESULTS

1.	Resynchronization group (n = 409)	Medical group (n = 404)
Primary end point	39%	55%
Deaths	20%	30%
Unplanned hospitalization	18%	33%
Worsening HF	47%	64%

(My estimated absolute difference = 15%; NNT = 7)

2. Resynchronization reduced the intraventricular mechanical delay and the end-systolic volume, and increased the left ventricular ejection volume. It improved symptoms and quality-of-life.
3. Adverse effects: Lead displacement; coronary sinus dissection; pneumothorax; infection.  
One patient in the CR group died of heart failure aggravated by lead displacement.

## DISCUSSION

1. CR substantially reduced the risk of complications and deaths among patients with HF due to left ventricular systolic dysfunction and cardiac dyssynchrony. The benefits were in addition to those afforded by pharmacologic therapy.
2. Over the study period, for every nine devices implanted, one death and 3 hospitalizations for major cardiovascular events were prevented. The reduction in risk of death is similar to that associated with beta-blocker therapy.
4. The extent to which risk can be modified may be greater among patients with less severe disease. CR may be beneficial in patients even if their symptoms are not severe.
5. Although a defibrillator was not implanted in this study, the CR group had a decreased incidence of sudden death. This may reflect the improvement in cardiac function. Retarding the progression of cardiac dysfunction to prevent malignant arrhythmias may be a better strategy than treating malignant arrhythmias once they occur.

## CONCLUSION

In patients with HF and cardiac dyssynchrony (left bundle branch block), cardiac resynchronization improved symptoms, and reduced complications and risk of death.

Benefits are in addition to standard pharmacologic therapy.

NEJM April 14,2005; 352: 1539-49 Original investigation by the Cardiac Resynchronization-Heart Failure (CARE-HF) Study Investigators, first author John G F Cleland, Castle Hill Hospital, Kingston-upon-Hull, UK

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*Enables The Ventricles To Contract Simultaneously.*

### **4-10 RESYNCHRONIZING VENTRICULAR CONTRACTION IN HEART FAILURE**

*(This editorial comments and expands on the preceding article)*

Up to 1/3 of patients with congestive heart failure (**HF**) have some form of intraventricular conduction abnormality. The most common pattern is left bundle branch block. (**LBBB**). In these patients electrical activation of the lateral aspect of the left ventricle can be substantially delayed in relation to that of the right ventricle and intraventricular septum. The dyssynchronous contraction is mechanically inefficient. The ejection fraction and cardiac output decrease, and HF becomes more severe.

The biventricular-pacemaker implantation is technically demanding. It provides atrial-based, biventricular stimulation. Three leads are placed to pace 1) the right atrium, the 2) right ventricle, and the 3) left ventricle. The left ventricular lead is inserted into the coronary sinus (in the right atrium) and advanced into a cardiac vein on the lateral wall of the lateral wall of the left ventricle. This enables the ventricles to contract simultaneously.

Complications of insertion are more frequent than for conventional pacemaker insertion. Considerable experience in the technique is required. Subsequent lead dislodgement occurs in as many as 10% of patients.

Many patients with HF for which resynchronization is indicated are also candidates for a cardioverter-defibrillator. Integrated devices are available capable of performing both functions.

The FDA currently approves use of cardiac-resynchronization therapy in patients with moderate-to-severe HF and intraventricular conduction delay.

NEJM April 14, 2005; 352: 1594-97 Editorial by John A Jarco

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*The Clinical Hallmark Is Fatigable Muscle Weakness Which Improves With Rest and Application Of Cold*

### **4-11 DOES THIS PATIENT HAVE MYASTHENIA GRAVIS?**

Delays in the diagnosis of myasthenia gravis (**MG**) may put patients at risk for complications. Clinicians must be able to diagnose the disease promptly. It is treatable.

MG is an autoimmune disease associated with circulating antibodies to acetylcholine receptors in muscle. Modification of the synaptic cleft and destruction of the postsynaptic neuromuscular membrane occur.



MG is rare. ~ 14/100 000. The diagnosis often is delayed for a year or more. The earlier treatment is started, the better the clinical response.

The clinical hallmark is fatigable muscle weakness.

Severity ranges from mild, purely ocular forms, and severe generalized weakness with respiratory failure.

The most specific diagnostic test is determination of the acetylcholine receptor antibody. But, some patients with the mild ocular form are negative for the antibody.

The authors of this study conducted a MEDLINE search to determine if items in the history and examination or results of simple tests would change the likelihood of MG being present. The search resulted in selection of 15 articles, which met inclusion criteria.

#### *Anatomical and physiological origins of the symptoms and signs:*

Normally, acetylcholine is released into the synaptic cleft, diffuses to the post-synaptic membrane, binds to ion channels, and causes an excitatory post-synaptic end-plate potential. If a threshold potential is achieved, an action potential spreads along the muscle fiber membrane. The muscle contracts.

Acetylcholine is cleared from the cleft by pre-synaptic reuptake and by the metabolic action of acetylcholinesterase.

In MG, failure of transmission at many neuromuscular junctions results in diminished end-plate potentials. Sustained or repetitive muscle contractions cause fatigue and weakness. Cooling a weak muscle improves transmission. Rest and acetylcholinesterase inhibitors transiently increase acetylcholine levels at the synapse. Strength is increased.

#### *Symptoms and signs and how to elicit them:*

Patients often complain of weakness in specific muscles. Commonly, the ocular muscles are the first to be affected. Patients develop double vision and drooping of the eyelids.

About ¼ present with bulbar weakness: slurred or nasal speech; alterations of the voice; difficulty chewing or swallowing.

Limb weakness is rarely an initial complaint.

The characteristic finding is reduced muscle power which worsens with repetition and improves with rest. Ptosis and extraocular muscle defects are relatively free of a voluntary component and provide a more objective measure. Fatigable and rapidly fluctuating asymmetric ptosis is a hallmark. Improvement may occur following even short periods of rest. The ptosis may shift quickly from one eye to the other. Test by having the patient sit and fix on a distant object. Ask the patient to refrain from blinking. The frontalis muscles should be relaxed. (Frontalis contraction is a mostly involuntary compensatory mechanism in MG patients with ptosis. Relaxing them may be difficult for the patient.) The palpebral fissure width is measured during forward gaze and again during upward and lateral gaze which the patients maintains for 30 seconds.

The more ptotic eye should then be used for further tests:

The ice pack test: Place a latex glove filled with crushed ice over the ptotic eyelid for 2 minutes.

The rest test: The patient places a glove filled with cotton (a placebo) over the more ptotic eyelid

while holding the eyes closed for 2 minutes.

The sleep test; Patient is placed in a dark room with his eyes closed for 30 minutes.

(Evaluate response immediately. Complete or almost complete resolution of the ptosis or at least a 2 mm increase in the width of the palpebral fissure constitutes a positive response to these maneuvers.)

The peek sign: detects orbicularis oculi weakness. After gentle closing of the eye, and complete apposition, within 30 seconds the lid margins separate and the sclera starts to show. (ie, weakness of the orbicularis prevents continuing closure of the lids.) The eyeballs roll up, so the iris is not seen.

Asymmetrical weakness of the extraocular muscles is common with sustained upward or lateral gaze. This induces double vision.

Tongue and pharyngeal weakness will result in speech becoming slurred, especially with prolonged speaking. Neither normal swallowing nor normal speech rules out MG.

#### *Anticholinesterase tests:*

Edrophonium is a fast- and short-acting anticholinesterase inhibitor. Its effect usually occurs within seconds and lasts less than 5 minutes. Serious adverse effects can occur. Atropine must be immediately available to counteract them. Primary care clinicians may defer to experts with experience in its administration. Unequivocal improvement in ptosis or extraocular muscles constitutes a positive response.

Neostigmine and pyridostigmine are other anticholinesterase agents. The latter is the most commonly drug used for the symptomatic treatment of MG.

#### *Analysis of the 15 articles reviewed:*

Accuracy of symptoms for diagnosis:

Neither normal swallowing nor normal speech rules out MG.

Accuracy of signs for the diagnosis of MG:

The peek sign might be a more useful sign. Likelihood ratio (LR) = 30

Accuracy of simple office tests:

Positive ice test (LR = 24)

Positive sleep test (LR = 53)

#### *Conclusions:*

“Fluctuating weakness that worsens with exertion and improves with rest or with application of ice or cold is never normal.” The fluctuation is dramatic and occurs rapidly.

Bear in mind that the initial fluctuating weakness of MG may become fixed over time if severe enough.

Certain historical features (speech becoming unintelligible after prolonged periods) of signs (peek test) maybe useful in diagnosis. Their absence does not rule it out.

The ice test, sleep test, and response to anticholinesterase agents are useful in confirming the diagnosis

A positive test result should prompt proceeding with acetylcholine receptor antibody testing and specialist referral.

JAMA April 20, 2005; 293: 1906-14 “The Rational Clinical Examination”, review article, first author Katalin Scherer, Duke University Medical Center, Durham, NC.

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*“Ask Your Doctor if X is Right for You”*

#### **4-12 DIRECT-TO-CONSUMER ADVERTISING**

##### ***A Haphazard Approach to Health Promotion***

The argument about direct-to-consumer advertising (**DTCA**) has continued ever since the FDA in 1997 relaxed the rules governing mass media advertising for prescription drugs. In the intervening years, researchers have published a substantial body of observational analyses of DTCA. The work has surveyed data of the \$3 billion-per-year uncontrolled experiment with DTCA in the US.

DTCA drives sales of newer, more expensive products for symptomatic relief of chronic conditions. The market potential is huge. Just 20 prescription drugs account for about 60% of the total industry spending on DTCA. Retail sales of the 50 drugs most heavily advertised to consumers increased an aggregate of 32% compared with 14% for all other drugs combined. Erectile dysfunction, arthritis, and allergies are the most common conditions advertised.

“Relying on emotional appeals, most advertisements provide a minimal amount of health information, describe benefits in vague, qualitative terms, and rarely offer evidence of support claims.”

The great majority of physicians believe that DTCA does not provide balanced information. The FDA rarely writes regulatory letters. “Millions of patients are exposed to misleading advertisements.” Nearly 80% of physicians think that DTCA encourages patients to seek treatments they do not need. Less than 10% of physicians consider DTCA a positive trend in health care.

According to surveys, up to 1/3 of adult patients each year talk to a physician about a health issue after seeing an advertisement.

DTCA has been associated with health service utilization for some conditions (eg, osteoporosis, dyslipidemia, seasonal allergies) but not for others (eg, hypertension).

Patient requests for prescription drugs appear to influence prescribing decisions. In about half of the cases, the physician prescribes the drug partly to accommodate a patient’s request. “There is no compelling evidence that this is inappropriate prescribing.” However, from the physician, patient, and public health perspectives, issues of safety and net benefit of DTCA remain controversial. This question remains unanswered. . . “Does DTCA motivate the right patients to seek the right care, or on balance, inordinately influence patients to seek unnecessary care.”

Highly advertised drugs which are used over the long-term by millions of persons may be associated with adverse effects not evident on trials (eg, *Vioxx*). In this case, DTCA was harmful.

“Decisions to advertise a specific product to the public do not necessarily reflect superior safety, efficacy, or the interests of the public health, but rather calculations of return on investment.”

The safety of a new drug cannot be known for certain until it has been on the market for several years. “The FDA should consider a moratorium on advertisement of drugs directly to consumers for 3 years after initial market release.”

If New Zealand passes a ban on DTCA in 2005 as anticipated, the United States will be the only industrialized country permitting such a practice.

JAMA April 27, 2005; 293: 2030-33 Editorial by Matthew F Hollon, University of Washington, Seattle.

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*Associated With A Slight Reduction In Days Of Heavy Drinking.*

#### **4-13 EFFICACY AND TOLERABILITY OF LONG-ACTING INJECTABLE NALTREXONE FOR ALCOHOL DEPENDENCE**

Worldwide, alcohol dependence (**AD**) is the fourth leading cause of disability. It is present in about 4% of the US adult population. AD is common among primary care patients.

Like diabetes, hypertension, and asthma, AD is a chronic disease in which genetic vulnerability, and social and environmental factors are involved in the etiology and course of the disease. Treatment is often ineffective.

The opioid antagonist naltrexone has been shown to be effective for treatment of AD. The FDA approved naltrexone in 1994 to treat AD after it was shown to reduce drinking frequency and likelihood of relapse to heavy drinking.

However, adherence to daily oral therapy is problematic, as it is with other medications.

Recently a new formulation of naltrexone has been made available. When given by injection, it releases the drug over a period of one month without daily peaks in concentration.

This study asks - Would monthly injections of long-acting naltrexone improve outcomes?

Conclusion: Long-acting naltrexone, given by injection once a month, was associated with a slight reduction in days of heavy drinking.

#### **STUDY**

1. A randomized, double-blind, placebo-controlled multicenter trial followed over 400 patients (mean age = 45). All were considered to be AD and almost all were still actively drinking (median heavy drinking days per month = 20). All were seeking treatment for their AD.
2. All had a history of heavy drinking during the 30 days before randomization. None had active hepatitis (AST or ALT greater than 3 times normal). None had a clinically significant medical condition or psychiatric disorder. None were known to be dependent on other drugs.
3. Detoxification prior to randomization was performed only if medically indicated.
4. Randomized to: 1) monthly injections of 380 mg long-acting naltrexone, or 2) placebo injections.
5. All also received low-intensity psychosocial intervention.
6. Follow-up = 6 months.

7. Primary analysis was by intention to treat.

## RESULTS

1. Only about 2/3 of subjects in the naltrexone group completed the trial. Of these, only 2/3 received all 6 injections.
2. Figure 3 (p 1623) illustrates a remarkable effect from “placebo” (motivation and counseling). In this group, over 6 months, median days of heavy drinking per month fell from about 19 at entrance to about 6.
3. Compared with placebo, in the naltrexone group, median days of heavy drinking fell by only about 3 additional days per month.
4. Men responded more favorably. Women did not benefit
5. Only 7% remained abstinent during the trial vs 5% in the placebo group. (Absolute difference = 2%; NNT (6 months) = 50.
6. Discontinuation due to adverse events occurred in 14% vs 7% in the placebo group. Nausea, fatigue, decreased appetite, dizziness were significantly more common in the naltrexone group.

## DISCUSSION

1. Long-acting injections of naltrexone, in conjunction with psychosocial treatment, reduced heavy drinking in this sample of treatment-seeking patients with AD. Patients who were abstinent when they began treatment benefited to a greater degree than those who were still drinking at the time of the first injection.
2. The authors believe that parenteral naltrexone may provide a basis for combination with other drug treatments.
3. The majority of clinical investigations of oral naltrexone required patients to be abstinent prior to starting medication. This study did not. Indeed, most patients in the trial were drinking heavily at enrollment. Many patients with AD who are actively drinking are motivated to reduce their drinking.
4. Patients who entered the trial with a goal of abstinence had a greater degree of drinking reduction than those who only intended to cut down.

## CONCLUSION

Monthly injections of long-acting naltrexone resulted in small reductions in heavy drinking among treatment-seeking AD patients.

JAMA April 6, 2005; 292: 1617-25 Original investigation, first author James C Garbutt, University of North Carolina, Chapel Hill

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*“May Lead To Treatment Which Slows Disease Progress”*

**4-14 GENE DISCOVERY PROVIDES CLUES TO CAUSE OF AGE-RELATED MACULAR DEGENERATION**

Age-related macular degeneration (**AMD**) is the most common cause of blindness in individuals over age 60 in the USA. Inflammation plays an important role in the etiology. AMD is progressive. It destroys the center of the macula and causes loss of the central field of vision.

Environmental factors (smoking, obesity, and fat intake) contribute to disease progression.

Currently there is no satisfactory treatment. There are a few measures that can slow progression for the dry to the more advanced wet form: laser therapy and high levels of antioxidants combined with zinc may slow progression.

Excessive complement activation occurs in AMD.

A gene variant may be responsible for about half of the 15 million cases of AMD in the US. Using techniques from the Human Genome Project, investigators have identified a common variant of the complement factor H (**CFH**) gene that explains about 50% of cases:

- A. The protein produced by normal CHF inactivates components of the alternate complement pathway. This leads to a reduction in likelihood of inflammation in the retina. (I.e, the normal CHF is a protective factor.)
- B. Individuals who possess a certain variant of the CFH gene are at increased risk of AMD. The protein [tyrosine replaced by histidine] encoded by the variant fails to bind to receptors on cells on the retina and surrounding blood vessels. The protective effect of normal CFH is lost. This leads to increased inflammation in the retina and choroid.

Discovery of this variant may lead to treatment which slows disease progress. A modest slow-down would be sufficient to preserve a patient's vision for the rest of his life.

JAMA April 20, 2005; 293: 1844-45 "Medical News and Perspectives" by Bridget M Kuehn, JAMA staff.