

# **PRACTICAL POINTERS**

## **FOR PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

**NOVEMBER 2003**

**THE CRUCIAL LINK BETWEEN LITERACY AND HEALTH**

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**DEMENTIA WITH LEWY BODIES**

**ACE INHIBITOR OR ANGIOTENSIN BLOCKER, OR BOTH. IN MYOCARDIAL INFARCTION**

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# NOVEMBER 2003

## HIGHLIGHTS AND EDITORIAL COMMENTS

### 11-1 THE CRUCIAL LINK BETWEEN LITERACY AND HEALTH.

In 1993, the National Adult Literacy Survey reported that half of adult Americans have limited literacy skills. They struggle to reliably complete many simple daily tasks such as completing forms, reading signs, or using transportation schedules. At least as many patients, then, must struggle with health care's many forms, educational materials, and directions.

"The physician should never presume that a patient is literate." Even the most poised and articulate persons may have trouble reading. People with reading problems are unlikely to step forward and ask for help.

One method to improve communication is called "closing the loop". The physician asks the patients to restate the message in their own words. This teach-back method assures the physician that the patient understands.

This is a good example of the large gap between "evidence based medicine" (EBM) and the real world of primary care. I do not recall reading in the entrance criteria of trials that all subjects were medically literate--nor in the exclusion criteria that those with poor literacy were excluded. I believe exclusion is automatic.

Randomized trials, the basis of EBM, deal with a well-defined group of subjects. Patients seen in primary care often do not fit into the group. This will require the clinician to use her best clinical judgment to fit the circumstances. As important as EBM is, I believe it does not apply to a large majority of clinic patients. RTJ

### 11-2 EFFECTS OF DIFFERENT BLOOD-PRESSURE-LOWERING REGIMENS ON MAJOR CARDIOVASCULAR EVENTS: OVERVIEW OF RANDOMIZED TRIALS

This study estimated the effects of strategies based on different drug classes and on those targeting different BP goals on the risks of major cardiovascular events and death.

Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events.

A larger reduction in BP reduces risk of total cardiovascular events. BP-lowering is a major component of the benefit conferred by the regimens investigated. There was a larger reduction in stroke and total major cardiovascular events from regimens aimed at a lower BP goal.

ACE-inhibitor-based regimens benefit across a wide range of hypertensive and non-hypertensive patients who are at high risk for cardiovascular disease.

ACE inhibitor or diuretic or beta-blocker are much more effective in preventing heart failure than calcium antagonists.

For stroke, there is a greater effect of regimens based on calcium antagonists than those based on diuretics or beta-blockers, but the results were of borderline significance.

Reductions in systolic BP of 2, 4, 6, 8, and 10 mmHg were associated with lower risk of stroke, major cardiovascular disease, coronary heart disease, cardiovascular death, and total mortality.

### 11-3 EMERGENCY CONTRACEPTION

Progestin alone has been approved by the FDA for emergency contraception (EC)—a total of 1.5 mg of levonorgestrel—two 0.75 mg tablets to be taken 12 hours apart (*Plan B*). (*Both tablets can be taken at once without loss of efficacy.*)

Pregnancy rates are lowest when EC is used within 12 hours of unprotected intercourse. Most studies report a monotonic decrement in effectiveness as the interval increases. Two studies have indicated that EC given within 5 days is still effective.

“Emergency contraception should thus be offered for any act of unprotected intercourse that has occurred in the preceding 5 days.” Because the day of ovulation is generally unknown, even in women who report regular cycles, treatment is indicated regardless of the cycle day on which unprotected intercourse occurred.

There are no absolute contraindications. Even in women who have contraindications to long-term use of birth control pills, the balance of risks and benefits favors the brief exposure of EC over the risks of pregnancy. Ectopic pregnancy has been reported, but there is no good evidence of increased risk.

The FDA is currently evaluating an application for over-the-counter status for the levonorgestrel-only formulation. It is highly suitable for such a switch. The dose is the same for everyone; no contraindications to use; adverse events are rare; no potential for addiction; repeated use is safe and reasonably effective. Use is highly acceptable to patients and is associated with high rates of continuation of oral contraceptives.

#### **11-4 STARTING EARLIER TO PREVENT HEART DISEASE.**

Two studies reported in the November 5 issue of JAMA measured carotid artery intima/media thickness (IMT) in young adults (age 24 to 37). LDL-cholesterol and BMI had been measured in childhood, up to 22 years earlier. Higher childhood levels of both predicted increased adult carotid IMT. In one study, systolic BP and smoking in adolescence also predicted increased IMT. (The higher the carotid IMT, the greater the extent of coronary atherosclerosis.)

It is clear that risk factors begin to matter during adolescence, the age range during which fatty streaks in the coronary arteries begin to be converted to raised lesions, and when high-risk populations begin to diverge from low-risk populations. “It may be possible that risk factors in the early teen-age years are associated with permanent damage to the arterial wall.”

Assessing risk factors in youth is easy and inexpensive. Cholesterol and other risk factors do matter during adolescence. It may now be time to reconsider the age at which measurement of cholesterol and life-style changes should begin. The difficulty of changing life styles in teenagers, however, should not be underestimated. Physicians caring for children and adolescents should be sure their patients and their parents know it is beneficial and safe to promote and maintain a healthy life style.

Changing ingrained life-style habits in teen-agers is almost impossible. Parents must set the example and begin lifetime habits of their children at a pre-teen age.

#### **11-5 A RANDOMIZED TRIAL OF LETROZOLE IN POSTMENOPAUSAL WOMEN AFTER FIVE YEARS OF TAMOXIFEN THERAPY FOR EARLY-STAGE BREAST CANCER**

Letrozole, an aromatase inhibitor, begun after 5-years of tamoxifen had been completed, significantly improved disease-free survival. Aromatase is the enzyme which converts the androgenic substrates, androstenedione and testosterone, into estradiol. Letrozole (*Femara*) is one of several new aromatase inhibitors (a third generation). This drug binds to the aromatase and almost completely inactivates it, thus providing maximal endocrine control of breast cancer (**BC**).

The aromatase inhibitors are challenging tamoxifen, the previous gold standard for treatment of postmenopausal women with estrogen-receptor-positive BC. In advanced BC, letrozole is clearly superior to tamoxifen as first-line therapy. Aromatase inhibitors are also being considered in chemoprevention, a strategy in which tamoxifen has already been shown to reduce incidence of BC.

Tamoxifen blocks the binding of estradiol to the BC cells. It has dual effects which are complex, both antagonistic and agonistic. After 5 years of treatment its agonistic effects may predominate. Aromatase inhibitors do not have agonistic effects.

There was also a reduction in the frequency of new primary BC in the contralateral breast (relative reduction of 46%).

## **11-6 EFFECT OF FIRMNESS OF MATTRESS ON CHRONIC NON-SPECIFIC LOW-BACK PAIN**

Randomized, double-blind, controlled, multicenter trial assessed 313 adults (median age 44) who had chronic low-back pain. None had referred pain. All complained of backache while lying in bed and on arising.

At 90 days, patients using the medium-firm mattress were about twice as likely to improve as were patients using firm mattresses.

Outcomes for less pain in bed (Odds Ratio = 2.4), less pain on arising (OR = 1.93) and less disability (OR = 2.1) as compared with the firm mattress.

Throughout the study, the medium-firm group had less daytime low-back pain.

“The results of this study suggest that, although psychosocial factors have an effect on disability, some biomechanical factors also have an effect and should be taken into consideration.”

How can the primary care clinician apply these results? I believe it comes down to a N of 1 study. If possible, patients may try a variety of mattresses. This may not be practical. If the patient considers his mattress to be firm, a less firm one may be tried. If he considers it to be soft, a firmer one may be tried.

## **11-7 STROKE PREVENTION WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN COMPARED WITH WARFARIN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION.**

Ximelagatran is a direct thrombin inhibitor which is given orally.. Its pharmacokinetic profile is predictable and stable overtime. It has low potential for drug-drug interactions and does not require monitoring or dose adjustment.

Fixed dose ximelagatran was at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism. It is much easier to use.

Practical Pointers has abstracted several articles on the new oral anticoagulant ximelagatran. (See October 2003 issue.)

Ximelagatran looks very promising.

## **11-8 EFFECTS OF PERIOPERATIVE ADMINISTRATION OF A SELECTIVE CYCLO-OXYGENASE 2 INHIBITOR ON PAIN MANAGEMENT AND RECOVERY AFTER KNEE REPLACEMENT.**

Perioperative (before and after surgery) use of a COX-2 inhibitor was effective component of multimodal analgesia. It reduced opioid consumption, pain, vomiting, and sleep disturbance. It shortened the time physical therapy was needed to achieve effective joint range of motion.

Pain is the 5<sup>th</sup> monitored vital sign. Efficient management of pain improves postoperative clinical outcomes. After total knee arthroplasty (TKA), inadequate control of postoperative pain is associated with poor functional recovery

Surgical trauma induces cyclo-oxygenase 2 (COX-2) which then promotes synthesis of prostaglandins that sensitize peripheral nociceptors and mediate central sensitization. NSAIDs as well as opioids decrease this inflammatory response. Pre-operative administration of NSAIDs may be effective by establishing a sufficient tissue NSAID concentration to inhibit early production of prostaglandins before the onset of tissue trauma, thus attenuating the development of hyperalgesia.

I wonder if sports medicine enthusiasts might offer pre-game COX-2 inhibitors to players (eg, football) who might be subject to injury during a game. This might lessen the period of disability if a serious injury should occur.

## **11-9 DIASTOLIC HEART FAILURE**

Diastolic heart failure (DHF) refers to the clinical syndrome of heart failure (HF) with a preserved left ventricular ejection fraction (0.50 and above) in the absence of major valvular disease. About a third of patients with HF seen by clinicians have DHF as so defined.

The pathophysiology of DHF is characterized by a *low cardiac output* resulting from impeded flow into the left ventricle caused by thick ventricular walls and a small ventricular cavity.

Clinically, patients with DHF are elderly, more likely female, and often have a raised BP and associated left ventricular hypertrophy. However, clinical characteristics by themselves cannot reliably distinguish systolic from diastolic HF. To make the distinction, it is therefore important to obtain an imaging study, typically echocardiography, to estimate left ventricular ejection fraction.

Mechanisms contributing to abnormal left ventricular diastolic properties include: stiff large arteries, hypertension, myocardial ischemia, and diabetes.

Acute treatment includes: BP control, relief of ischemia, control of ventricular rate in patients with atrial fibrillation. Chronic treatment includes restriction of dietary sodium, and control of hypertension. Treatment is largely empirical.

## **11-10 END-OF-LIFE CARE AND THE EFFECTS OF BEREAVEMENT ON FAMILY CAREGIVERS OF PERSONS WITH DEMENTIA**

Caregivers in this study showed remarkable resilience in adapting to the death of their relatives. A large majority reported feeling relieved by the death, although persons whose relatives were institutionalized did not show as rapid a recovery from depressive symptoms. This suggests that relief from providing daily care did not alone account for the caregivers' recovery from bereavement.

Investments in resources for intervention and support may have the largest benefit when they are applied to caregivers and patients in the period immediately preceding the patient's death. When caregivers know that their relative is on a trajectory toward death, and when they are aware of the patient's disability and suffering, they grieve for the loss of the patient before the death.

Clinicians should view bereavement not only as a phenomenon that affects caregivers after the death, but also as one that affects many caregivers before the death occurs.

## **11-11 DEMENTIA WITH LEWY BODIES**

Dementia with Lewy bodies (**DLB**) is one of the 3 most common causes of dementia in older people. Alzheimer's disease and vascular dementia are the other two.

The clinical presentation of DLB typically includes: fluctuating cognitive impairment, visuospatial dysfunction, marked attention deficits, psychiatric symptoms (especially complex visual hallucinations), and mild extrapyramidal features. DLB can usually be differentiated from Parkinson's disease with dementia because in DLB the motor symptoms usually develop *after* the cognitive impairment. Some authorities require, as a diagnostic criterion for Parkinson's disease, a delay of at least 12 months between the onset of motor symptoms and subsequent cognitive impairment.

My dictionary defines Lewy body as an eosinophilic inclusion body found in the cytoplasm of neurons in the cortex and brain stem in Parkinson's disease and some forms of dementia. But, as I understand it, DLB is not a form of Parkinsonism, although when dementia occurs in Parkinsonism, the two may be confused. The pathology differs.

There is a "need to maintain a high degree of awareness of DLB especially when prescribing neuroleptic drugs for people whose dementia is characterized by early psychiatric symptoms." Neuroleptic drugs (more simply anti-psychotic drugs) include phenothiazines. (eg, chlorpromazine [*Thorazine*], thioridazine, perphenazine, fluphenazine). Severe neuroleptic sensitivity reactions may occur.

DLB may respond to cholinesterase inhibitors.

I abstracted this short article to learn more about Lewy dementia. I had not understood much about it.

Still, making the diagnosis does not help the patients much.

## **11-12 VALSARTAN, CAPTOPRIL, OR BOTH IN MYOCARDIAL INFARCTION COMPLICATED BY HEART FAILURE, LEFT VENTRICULAR DYSFUNCTION, OR BOTH**

Angiotensin-converting-enzyme inhibitors (**ACE-I**) do not completely block production and effects of angiotensin II. Likewise, angiotensin-receptor blockers (**ARB**) do not completely block angiotensin II. But, they do act differently. Investigators have speculated that adding the two would produce greater benefits than either one used alone.

In this study, however, use of the two drugs together did not benefit any more than either used alone. Valsartan is as effective as captopril (but not more effective) as measured by risk of death in patients who are at high risk for cardiovascular events after a myocardial infarction. The combination increased adverse effects without improving survival.

I abstracted this study because it contrasts with other studies reported in *Practical Pointers*. Doubt remains about the efficacy of combined ACE inhibitors and ARBs. See “Effects of Candesartan on Mortality and Morbidity in Patients with Chronic Heart Failure” *Practical Pointers* September 2003. The study reported a slight benefit when candesartan was added to ACE inhibitors. (NNT = 25 to 50) Hyperkalemia, hypotension, and increased creatinine levels occurred more commonly in the combined group.

I believe primary care clinicians should avoid the combination until clarification is available. ARB may be used when ACE inhibitors are not tolerated. RTJ

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### ***“About Half Of The Hospital’s Patients Could Not Read.”***

#### **11-1 THE CRUCIAL LINK BETWEEN LITERACY AND HEALTH.**

In the early 1990s Ruth Parker, an internist practicing at Grady Hospital in Atlanta, became interested in the waiting times in the emergency department. Surprisingly, some patients completed the rather long surveys in just a few minutes. There was no way this could be done so quickly. The reason was that these patients were not reading the survey at all—they were simply haphazardly answering the multiple choice questions. Further inquiry discovered that about half of the hospital’s patients could not read.

In 1993, the National Adult Literacy Survey proved that this estimate was correct. Half of adult Americans have literacy skills that are limited, or even worse, meaning that they struggle to reliably complete many simple daily tasks such as completing forms, reading signs, or using transportation schedules.

At least as many patients, then, must struggle with health care’s many forms, educational materials, and directions.

There is a link between health and literacy. Literacy skills predict an individual’s health status more strongly than age, income, employment status, education level, and racial and ethnic group. Literacy directly affects patients’ ability to follow instructions, read pill bottle labels, take medications properly, understand disease-related information, learn about disease prevention and self management, and to understand their rights. Illiteracy affects patient’s ability to access care. It increases chances of dying from chronic and communicable disease. People with low literacy have high hospitalization rates. Low literacy is prevalent among primary care patients and among core patient groups such as the elderly and others with chronic conditions. Low-literacy patients with diabetes are less likely to obtain good glycemic control. Those with asthma have poor metered-dose inhaler techniques. Those with HIV have lower CD4 cell counts.

“The physician should never presume that a patient is literate.” Even the most poised and articulate persons may have trouble reading. People with reading problems are unlikely to step forward and ask for help.

Although many native-born Americans have poor literacy, it is generally higher among the elderly and among ethnic and racial minorities in public hospitals and clinics. Experts advise approaching all patients as if they have a lower level of functional health literacy and communicate accordingly.

Most medical information on the Internet is written at a 12<sup>th</sup> grade level. The average American reads at about the 9<sup>th</sup> grade level--the average Medicaid recipient at the 5<sup>th</sup> grade level. Patients often comprehend as little as half of what physicians tell them.

One communication method called “closing the loop” is for the physician to ask patients to restate the message in their own words. This teach-back method assures the physician that the patient understands.

The U.S. Health and Human Services and the WHO have made health literacy research and interventions a priority.

Suggestions for patients to get the most out of a doctor visit

I will ask 3 questions:

1. What is my main problem?
2. What do I need to do?
3. Why is it important to do this?

I will bring a friend or family member to help me at the visit.

I will make a list of my health concerns to tell my doctor

I will bring a list of all my medicines

I will ask my pharmacist for help when I have questions about my medicines.

Annals Int Med November 18, 2003; 139: 875-78 “Current Clinical Issues”, editorial by Jennifer Fisher Wilson.

Comment:

This is a good example of the large gap between “evidence based medicine” (EBM) and the real world of primary care. I do not recall reading in the entrance criteria of trials stating that all subjects were medically literate--nor in the exclusion criteria that those with poor literacy were excluded. I believe exclusion of these patients is automatic.

Randomized trials, the basis of EBM, deal with a well defined group of subjects. Patients seen in primary care often do not fit into the group. This will require the clinician to use her best clinical judgment to fit the circumstances. As important as EBM is, I believe it does not apply to a large majority of clinic patients. RTJ

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*Any Commonly-Used Regimen Reduces Risk The Greater The BP Lowering, The Lesser The Risk*

## **11-2 EFFECTS OF DIFFERENT BLOOD-PRESSURE-LOWERING REGIMENS ON MAJOR CARDIOVASCULAR EVENTS: OVERVIEW OF RANDOMIZED TRIALS**

About two-thirds of the cardiovascular disease burden and half the ischemic heart disease burden are attributable to non-optimum blood pressure. The beneficial effects of BP-lowering on risks of major cardiovascular events are well established. Uncertainty remains about the comparative effects of different

BP-lowering regimens and of regimens targeting different BP goals.

The uncertainty about the comparative effects of different regimens in part reflects the limited statistical power of most individual studies to identify plausible differences in the size of treatment effects, differences between studies in selection of patients, choice of outcome definitions, and achieved BP reductions.

This study estimated the effects of strategies based on different drug classes and on those targeting different BP goals on the risks of major cardiovascular events and death.

Conclusion: Treatment with *any* commonly used regimen reduces the risk of total major cardiovascular events. Larger reductions in BP produce larger reductions in risk.

## STUDY

1. Systematic review of 29 randomized trials included over 160 000 persons ( mean age 65). Inclusion criteria:
  - 1) random allocation to either a BP-lowering drug or placebo, 2) random allocation to different BP goals, and 3) random allocation to regimens based on different classes of BP-lowering drugs.
2. Patients were selected mainly on the basis of high BP, diabetes, coronary heart disease, peripheral vascular disease, cerebrovascular disease or renal disease.
3. For every comparison, tested the null hypothesis of no difference between 6 predefined outcomes: stroke, coronary heart disease, heart failure, major cardiovascular events, death from any cardiovascular event, and total mortality.

## RESULTS

1. Treatment with any commonly-used regimen reduced the risk of total major cardiovascular events.
2. Outcomes:

	Active drug vs placebo		Drug vs drug	
	Relative risk		Relative risk	
A. Stroke				
ACE inhibitor vs placebo	0.72	ACE-I vs D/BB*	1.09	
Calcium antagonist vs placebo	<u>0.62</u>	CA vs D/BB	<u>0.93</u>	
More BP-lowering vs less	0.77	ACE-I vs CA	1.12	
B. Coronary heart disease				
ACE inhibitor vs placebo	0.80	ACE-I vs D/BB*	0.98	
Calcium antagonist vs placebo	0.78	CA vs D/BB	1.01	
More BP-lowering vs less	0.95	ACE-I vs CA	0.96	
C. Heart failure				
ACE inhibitor vs placebo	0.82	ACE-I vs D/BB*	1.07	
Calcium antagonist vs placebo	<u>1.21</u>	CA vs D/BB	<u>1.33</u>	
More BP-lowering vs less	0.84	ACE-I vs CA	<u>0.82</u>	
D. Major cardiovascular events				
ACE inhibitor vs placebo	0.78	ACE-I vs D/BB*	1.02	
Calcium antagonist vs placebo	0.82	CA vs D/BB	1.04	

More BP-lowering vs less	0.85	ACE-I vs CA	0.97
E. Cardiovascular death			
ACE inhibitor vs placebo	0.80	ACE-I vs D/BB*	1.03
Calcium antagonist vs placebo	0.78	CA vs D/BB	1.05
More BP-lowering vs less	0.95	ACE-I vs CA	1.03
F. Total mortality			
ACE inhibitor vs placebo	0.88	ACE-I vs D/BB*	1.00
Calcium antagonist vs placebo	0.78	CA vs D/BB	0.99
More BP-lowering vs less	0.96	ACE-I vs CA	1.04

(\* = diuretic or beta-blocker)

## 2. The main outliers:

Calcium antagonists more favorable in preventing stroke; less favorable in preventing heart failure.

## DISCUSSION

1. Treatment with any commonly-used regimen reduces the risk of total major cardiovascular events.
2. A larger reduction in BP reduces risk of total cardiovascular events.
3. ACE-inhibitor-based regimens benefit across a wide range of hypertensive and non-hypertensive patients who are at high risk for cardiovascular disease.
4. ACE inhibitor or diuretic or beta-blocker are much more effective in preventing heart failure than calcium antagonists.
5. For stroke, there is a greater effect of regimens based on calcium antagonists than those based on diuretics or beta-blockers, but the results were of borderline significance.
6. BP-lowering is a major component of the benefit conferred by the regimens investigated. There was a larger reduction in stroke and total major cardiovascular events from regimens targeting for a lower BP goal.
7. Reductions in systolic BP of 2, 4, 6, 8, and 10 mmHg were associated with lower risk of stroke, major cardiovascular disease, coronary heart disease, cardiovascular death and total mortality.

## CONCLUSION

Treatment with any commonly-used regimen reduces risk of total major cardiovascular events. Larger reductions in BP produce larger reductions in risk.

Lancet November 8, 2003; 362: 1527-35 Original investigation, by the Blood Pressure Lowering Treatment Trialists' Collaboration, reporter by Fiona Turnbull, University of Sydney, Australia.

### Comment:

The main point is to reduce the BP, both in patients with hypertension, and those without hypertension who have other risk factors for cardiovascular disease. The article did not mention combined use of two or three or more antihypertension drugs. This would be the most common approach in primary care practice. For long-term care, most primary care clinicians would start with the lowest dose of the least expensive drug. This would be generics: diuretic, beta-blocker, and ACE-I.

But, BP control is only a part of prevention. Other interventions must be added to maximize benefit: lipid lowering, aspirin, blockade of the renin-angiotensin-aldosterone system. RTJ

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## ***Millions Of Abortions Could Be Prevented Each Year***

### **11-3 EMERGENCY CONTRACEPTION**

*(Practical Pointers previously abstracted several articles on emergency contraception. I repeat because of its clinical significance. RTJ)*

About 3 million unintended pregnancies occur in the USA each year. Most result from non-use of contraception, or from contraception failure (eg, a broken condom). Emergency contraception (**EC**) could prevent these pregnancies. *(And lowers incidence of abortions. RTJ)*

During the most fertile period in young women (ages 19 to 26), a single act of unprotected intercourse occurring about one to two days before ovulation may result in a 50% chance of pregnancy. Immediate use of an emergency contraceptive will reduce risk of pregnancy to 1 to 2 percent.

Because sperm can survive in the female genital tract for 5 to 6 days, fertilization may occur days after sexual activity. Even the most sensitive pregnancy test will not be positive until after the implantation of a fertilized egg, an event that occurs about 7 days after fertilization.

Which EC to use?

- 1) The FDA has approved 100 ug ethinyl estradiol and 0.5 mg levonorgestrel to be given twice 12 hours apart (*Preven; Ovral*). [A total of 4 tablets]
- 2) The same efficacy can be attained by use of birth control pills that combine norgestrel 1.0 mg, or levonorgestrel 0.5 mg, along with 100 ug of ethinyl estradiol. (Total of 2 pills 12 hours apart.)
- 3) Progestin only (also FDA approved) a total of 1.5 mg of levonorgestrel—two 0.75 mg tablets to be taken 12 hours apart. (*Plan B*) {Both tablets can be taken at once without loss of efficacy.}

Adverse effects;

Nausea may occur in up to 50% and vomiting in about 20%.

Timing of use:

Pregnancy rates are lowest when EC is used within 12 hours of unprotected intercourse. Most studies report a monotonic decrement in effectiveness as the interval increases. Two studies have indicated that EC given within 5 days is still effective. “Emergency contraception should thus be offered for any act of unprotected intercourse that has occurred in the preceding 5 days.” Because the day of ovulation is generally unknown even in women who report regular cycles, treatment is indicated regardless of the cycle day on which unprotected intercourse occurred.

Safety:

Thrombotic events have *not* been reported.

There are no absolute contraindications. Even in women who have contraindications to long-term

use of birth control pills, the balance of risks and benefits favors the brief exposure of EC over the risks of pregnancy. Ectopic pregnancy has been reported, but there is no good evidence of increased risk.

Does EC have adverse effects if pregnancy is already established but not diagnosed?

. A large WHO study of 2000 treatments reported 42 pregnancies. None were ectopic. Five were continued with normal outcomes. No study is large enough to quantify the teratogenic risk. Observations that there is no increase in birth defects among women who take combined BC pills are reassuring. EC does not interfere with an established post-implantation pregnancy.

Advance prescribing:

EC is currently available only by prescription. This may delay taking it. Clinicians can help prevent this problem by providing EC in advance of need. Studies of this approach report that advanced provision increased use, that the use was appropriate, that women did not abandon or decrease use of their regular contraceptives, and that the number of pregnancies was reduced.

The FDA is currently evaluating an application for a switch to over-the-counter status for the levonorgestrel-only formulation. EC is highly suitable for such a switch. The dose is the same for everyone; no contraindications to use; adverse events are rare; no potential for addiction; repeated use is safe and reasonably effective. Use is highly acceptable to patients and is associated with high rates of continuation of oral contraceptives.

Conclusion:

The preferred regimen is the levonorgestrel-only product at a single dose of 1.5 mg. If supplies are not available in the physician's office, the physician should be able to identify a pharmacy that stocks this product. The physician should provide separate prescriptions to be used if unprotected intercourse occurs again. The use of regular contraception should be emphasized, along with condom use to reduce risk of sexually transmitted diseases. Eligible women should include those who are not currently sexually active, since they are unlikely to have no ongoing method of contraception and are at risk if they become sexually active.

NEJM November 6, 2003; 349: 1830-35 "Clinical Practice", commentary by Carolyn Westhoff, Columbia University, New York.

Comment:

The FDA is on the verge of approving EMC for availability over-the-counter

The article sidestepped the debate about ethical use of EC. I believe most of us understand that EC does not cause abortion since pregnancy is not established at the time of use and EC will not disturb an already established pregnancy. Some disagree, and believe pregnancy begins at fertilization. I doubt this controversy will be settled anytime soon, RTJ

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***Prevention Should Begin At An Early Age***

**11-4 STARTING EARLIER TO PREVENT HEART DISEASE**

Recently, non-invasive imaging (eg, ultrasound) has become available to measure atherosclerosis in accessible arteries. The intima-media thickness (IMT) of the carotid arteries parallels coronary artery atherosclerosis. Childhood total cholesterol levels and body mass index are associated with increased IMT in early adulthood. Two studies reported in this issue of JAMA <sup>1,2</sup> measured IMT in young adults (age 24 to 37). LDL-cholesterol and BMI had been measured in childhood, up to 22 years earlier. Both predicted increased adult carotid IMT. In one study, systolic BP and smoking in adolescence also predicted increased IMT.

It has been known for over 50 years that atherosclerosis begins in childhood and progresses through adolescence and young adulthood to cause coronary heart disease (CHD) in middle age and later. High prevalence and rapid progression of raised lesions can occur in the fatty streaks in the coronary arteries of adolescents and young adults. The extent of raised lesions (ie, fibrous plaques and complicated lesions) in the coronary arteries of adults parallels the incidence of CHD. The difference between raised lesions in populations with high rates of CHD and those with low rates becomes evident by age 25. Risk factors for coronary atherosclerosis are often present in individuals with raised lesions.

It is clear that risk factors begin to matter during adolescence, the age range during which fatty streaks begin to be converted to raised lesions, and when high-risk populations begin to diverge from low-risk populations. “It may be possible that risk factors in the early teen-age years are associated with permanent damage to the arterial wall.”

Weaker and less-consistent associations were observed in women compared with men. Between age 15 and 34, women lag about 5 to 10 years behind men in the development of raised lesions.

Assessing risk factors in youth is easy and inexpensive. It may now be time to reconsider the age at which measurement of cholesterol and lifestyle changes should begin. The difficulty of changing life styles in teenagers, however, should not be underestimated. Physicians caring for adolescents should be sure their patients and their parents know it is good and safe to promote and maintain a healthy lifestyle.

Atherosclerosis and CHD are at least partially preventable.

JAMA November 5, 2003; 290: 2320-22 Editorial, first author Henry C McGill Jr., University of Texas Health Science Center, San Antonio.

1 “Childhood Cardiovascular Risk Factors And Carotid Vascular Changes In Adulthood: The Bogalusa Hear Study.”

2 “Cardiovascular Risk Factors In Childhood And Carotid Artery Intima-Media Thickness In Adulthood. The Cardiovascular Risk In Young Finns Study”

Comment:

Changing ingrained life-style habits in teen-agers is almost impossible. Parents must set the example and begin lifetime habits of their children at a pre-teen age. RTJ

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***Aromatase Inhibitor Effectively Extends Disease-Free Survival After 5-Years Of Tamoxifen.***

**11-5 A RANDOMIZED TRIAL OF LETROZOLE IN POSTMENOPAUSAL WOMEN AFTER FIVE YEARS OF TAMOXIFEN THERAPY FOR EARLY-STAGE BREAST CANCER**

The risk of recurrence of breast cancer (BC) continues for an indefinite period of time after surgery, radiation and medical therapy. Growth depends on the action of estrogen. Long-term reductions in risk of recurrence have been achieved by antagonizing estrogen.

In hormone-receptor-positive BC, post operative use of five years of tamoxifen (*Nolvadex*) prolongs risk of recurrence by 47% and reduces risk of death by 26%. Prolonging it beyond 5 years does not benefit. Tamoxifen has both antagonistic and partial agonistic actions on BC. Over time, its agonistic action may be exaggerated. Thus outcomes are worse in women who continue after 5 years than in women who discontinue. The National Cancer Institute has recommended that tamoxifen be limited to 5 years.

Aromatase (estrogen synthase) convert precursors (androstenedione and testosterone) to estradiol.

Aromatase inhibitors (eg, letrozole) suppress estrogen production almost completely. In women with metastatic BC that progresses despite tamoxifen therapy, aromatase inhibitors, including letrozole, have demonstrated efficacy.

This study asked if letrozole begun after 5 years of tamoxifen therapy had been completed would have anti-tumor effects.

Conclusion: Letrozole, begun after 5-years of tamoxifen had been completed, significantly improved disease-free survival.

**STUDY**

1. Phase 3, randomized, double-blind, placebo-controlled trial entered over 5000 postmenopausal women with BC (mean age 62). All BCs were estrogen-receptor positive.. Primary surgery was considered adequate in all. About half had a lumpectomy and half a mastectomy. Axillary dissection was done in almost all. Many received adjuvant radiation therapy or adjuvant chemotherapy.
2. All the women had primary BC and had completed 5 years of tamoxifen therapy. Tamoxifen was discontinued.
3. Randomized to: 1) letrozole, or 2) placebo.
4. Primary end point = disease-free survival: secondary endpoints included overall survival and long term safety.
5. Planned follow-up = 5 years. (Ie, years 6 to 10 years after 5 years of tamoxifen)

**RESULTS**

1. Median follow-up = 2.4 years. The committee recommended the trial be terminated because of its favorable results.

2. Outcomes	Letrozole (n = 2575)	Placebo (n = 2582)
Recurrences of BC (local or metastatic)	75 women	132 women
Estimated 4-year disease-free survival	93%	87% *
Total deaths	31 women	42 women (not significant)
BC deaths	9 women	17 women

Overall survival 96.0 % 93.6 % \*\*

(\* NNT = 17. \*\* NNT = 42)

3. Adverse effects: low grade hot flashes, arthritis, arthralgia, myalgia were more frequent in the letrozole group. New diagnosis of osteoporosis 5.8% in the letrozole group vs 4.5% in the placebo group.

## DISCUSSION

1. This study compared therapy with the aromatase inhibitor letrozole vs placebo in healthy postmenopausal women with previously treated early BC. Letrozole was given from years 6 through 10 after the diagnosis, a period when tamoxifen is no longer beneficial, but when relapses of BC can occur.
2. Disease-free survival was improved in the letrozole group, including a substantial reduction in the rate of distant metastases. This . . .”confirms the continuous dependence of hormone-receptor-positive BC on estrogen.”
3. There was also a reduction in the frequency of new primary BC in the contralateral breast (relative reduction of 46%).
4. By decreasing estrogen levels, aromatase inhibitors may reduce bone mineral density by increasing bone resorption. They may also cause hypercholesterolemia.
5. Few women discontinued letrozole because of adverse effects which included hot flashes, arthritis, arthralgia, and myalgia (all generally low grade).
6. “Postmenopausal women with hormone-receptor-positive tumors who have completed about 5 years of adjuvant tamoxifen therapy should be considered for letrozole treatment.” The optimal duration of therapy and ultimate toxicity of almost complete estrogen deficiency is to be determined.
7. These results do not apply to premenopausal women. Aromatase inhibitors do not adequately suppress estrogen production in women who are still ovulating.

## CONCLUSION

As compared with placebo, letrozole therapy, after the completion of standard tamoxifen therapy, significantly improved disease-free survival.

NEJM November 6, 2003; 349: 1793-802 Original investigation, first author Paul E Goss, Princess Margaret Hospital, Toronto, Canada.

NEJM June 12, 2003; 2431-42 published a review article, “Aromatase Inhibitors in Breast Cancer” first author Ian E Smith Royal Marsden Hospital and Institute of Cancer Research, London, UK. This clarified my understanding of aromatase and aromatase inhibitors. See also editorial in the November 6 issue of NEJM pp 1855-59

Aromatase is the enzyme which converts the androgenic substrates, androstenedione and testosterone, into estradiol. Letrozole (*Femara*) is one of several new aromatase inhibitors (a third generation). This drug binds to the aromatase and almost completely inactivates it, thus providing maximal endocrine control of BC.

The aromatase inhibitors are challenging tamoxifen, the previous gold standard for treatment of postmenopausal women with estrogen-receptor-positive breast cancer (BC). In advanced BC, letrozole is clearly superior to tamoxifen as first-line therapy. Aromatase inhibitors are also being considered in chemoprevention, a strategy in which tamoxifen has already been shown to reduce incidence of BC.

Tamoxifen blocks the binding of estradiol to the BC cells. It has dual effects which are complex, both antagonistic and agonistic. After 5 years of treatment its agonistic effects may predominate. Aromatase inhibitors do not have any agonistic effects.

The long-term effects of profound estrogen suppression in postmenopausal women are unknown.

Comment:

I believe it likely that aromatase inhibitors may in the future supplant tamoxifen completely, both as preventive therapy and as first-line therapy after surgery for the primary lesion. RTJ

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### ***Medium-Firm Better Than Firm***

#### **11-6 EFFECT OF FIRMNESS OF MATTRESS ON CHRONIC NON-SPECIFIC LOW-BACK PAIN**

Non-specific low-back pain is defined as pain between the costal margins and the inferior gluteal folds that is generally accompanied by painful limitation of motion, is affected by physical activities and posture, and might be associated with referred pain. This implies that the syndrome is not related to underlying disorders, such as fractures, spondylitis, direct trauma, or systemic processes. In 85% of patients no organic cause can be established. Few treatments are effective.

Characteristics of the mattress may trigger pain, especially in the morning. Feeling back pain in bed or on rising in the morning are the factors most strongly associated with low-back pain.

Almost all orthopedic surgeons believe that mattresses play a part in the management of low-back pain. Many believe a firm mattress will relieve symptoms. Evidence supporting this is lacking.

This study assessed the effect of mattresses of different firmness on the clinical course of chronic low-back pain and disability.

Conclusion: A medium-firm mattress was superior.

#### **STUDY**

1. Randomized, double-blind, controlled, multicenter trial assessed 313 adults (median age 44) who had chronic low-back pain. None had referred pain. All complained of backache while lying in bed and on arising.
2. Rated firmness of mattresses on a scale developed by the European Committee for Standardization. (1.0 = firmest; 10.0 = softest).
3. Randomized to 1) a firm mattress [firmness 2.5] and 2) a medium-firm mattress [firmness 5.6].
4. Assessed clinical status at baseline and at 90 days.
5. Primary endpoints = improvements in pain while lying in bed, pain of arising, and disability.

#### **RESULTS**

1. At 90 days, patients using the medium-firm mattress were about twice as likely to improve as were patients using firm mattresses.
2. Outcomes for less pain in bed (Odds Ratio = 2.4), less pain on arising (OR = 1.93) and less disability (OR = 2.1) as compared with the firm mattress.
3. Throughout the study, the medium-firm group had less daytime low-back pain.

## DISCUSSION

1. In patients with low-back pain, mattress conditions affect the degree of pain-related disability and intensity while lying in bed and on arising.
2. In previous studies, substitution of old mattresses with firm and medium-firm new ones was associated with more frequent discontinuation of drug treatments and relative improvements in pain and disability
3. The underlying mechanism may be the effect of the firmness on pressure distribution and muscular function when lying in bed.
4. “The results of this study suggest that, although psychosocial factors have an effect on disability, some biomechanical factors also have an effect and should be taken into consideration.”

## CONCLUSION

A mattress of medium firmness improved back pain and disability (as compared with a firmer mattress) among patients with chronic low-back pain.

Lancet November 15, 2003; 362: 1599-1604 Original investigation, first author Francisco M Kovacs, Kovacs Foundation, Palma de Mallorca, Spain.

Comment:

How can the primary care clinician apply these results? I believe it comes down to a N of 1 study. If possible patients may try a variety of mattresses. This may not be practical. However, if the patient considers his mattress to be firm, a less firm one may be tried. If he considers it to be soft, a firmer one may be tried.

I do not know if mattress manufacturers in the USA have any standardization for firmness. The study used a firmness in the middle range—about 5 to 6 between 1 and 10.

My local mattress company offers 12 grades of firmness. They allow customers to try each one in the shop.  
RTJ

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### ***Ximelagatran Still Looks Good***

#### **11-7 STROKE PREVENTION WITH ORAL DIRECT THROMBIN INHIBITOR XIMELAGATRAN COMPARED WITH WARFARIN IN PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION.**

*(Practical Pointers has abstracted several articles on the new oral anticoagulant ximelagatran. I abstract this briefly to add another possible indication. RTJ)*

Adjusted dose warfarin provides highly effective prophylaxis against thromboembolism and ischemic stroke in patients with non-valvular atrial fibrillation (AF). Careful monitoring of dose is required.

Ximelagatran is a direct thrombin inhibitor which is given orally.. Its pharmacokinetic profile is predictable and stable over time. It has low potential for drug-drug interactions and does not require monitoring or dose adjustment.

This study randomized over 3400 patients with non-valvular AF and one or more risk factor for stroke to: 1) Ximelagatran 36 mg twice a day, or 2) Warfarin aimed at an INR of 2.0 to 3.0. Primary endpoint was stroke or systemic embolism.

Results: Over a mean of 17 months, 56 patients in the warfarin group and 40 in the ximelagatran group had a primary endpoint (2.3% per year vs 1.6% per year). Rates of disabling or fatal stroke, mortality, and major bleeding were similar between groups. Combined major and minor bleeding favored ximelagatran—26% vs 30%. Raised serum alanine aminotransferase was more common in the ximelagatran group.

Fixed dose ximelagatran was at least as effective as well-controlled warfarin for prevention of stroke and systemic embolism.

Lancet November 22, 2003; 362: 1691-98 Original investigation, by the Stroke Prevention using an Oral Thrombin Inhibitor in atrial fibrillation (SPORTIF) investigators reported by S Bertil Olsson, University Hospital, Lund, Sweden.

Comment:

See *Practical Pointers* October 2003 for several other articles about Ximelagatran. RTJ

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### ***Preemptive Analgesia Reduces Pain***

## **11-8 EFFECTS OF PERIOPERATIVE ADMINISTRATION OF A SELECTIVE CYCLO-OXYGENASE 2 INHIBITOR ON PAIN MANAGEMENT AND RECOVERY AFTER KNEE REPLACEMENT.**

Pain is the 5<sup>th</sup> monitored vital sign. Efficient management of pain improves postoperative clinical outcomes. Inadequate control of postoperative pain is associated with poor functional recovery after total knee arthroplasty (TKA).

Surgical trauma induces cyclo-oxygenase 2 (COX-2) which then promotes synthesis of prostaglandins that sensitize peripheral nociceptors and mediate central sensitization. NSAIDs as well as opioids decrease this inflammatory response. *Pre-operative* administration of NSAIDs may establish a sufficient tissue NSAID concentration to inhibit production of prostaglandins. If this occurs before the onset of tissue trauma, development of hyperalgesia may be attenuated.

Non-selective NSAIDs are associated with increased postoperative bleeding. This limits their use. Selective COX-2 inhibitors have little or no effect on coagulation and thus may be used in surgical settings. Rofecoxib (*Vioxx*) has been approved for treatment of acute postoperative pain.

Analgesic therapy initiated preemptively and continued postoperatively may reduce both incisional and inflammatory pain as well as peripheral and central neural sensitization. It may improve outcome. This study tested this hypothesis.

Conclusion; Perioperative use of a COX-2 inhibitor effectively reduced postoperative pain, consumption of opioids, vomiting, and sleep disturbance, and improved range of motion after TKA. .

## STUDY

1. Randomized, placebo-controlled double-blind trial enrolled 70 patients undergoing TKA.
2. Randomized to: 1) oral rofecoxib 50 mg at 24 hours and at 1 to 2 hours *before* surgery, and daily for 5 days postoperatively, followed by 25 mg for another 8 days, or 2) matching placebo.
3. Main outcome measures = postsurgical analgesic consumption, pain scores, nausea and vomiting, joint range of motion, sleep, and patient satisfaction.

## RESULTS

1. Outcomes:	Placebo	Rofecoxib
Total epidural analgesic 42-hour consumption	303 mL	252 mL
Daily postoperative opioid	9.3 mg	5.8 mg
Daily pain scale scores (visual analogue scale)	3.5	2.2
Nausea	44%	24%
Vomiting	25%	6%

Range of motion—earlier achievement of 90<sup>0</sup> knee flexion in the rofecoxib group.

Sleep disturbance—less on the first 3 nights in the rofecoxib group.

Satisfaction higher in the rofecoxib group.

2. Adverse events: None had any bleeding complications requiring therapy.

## DISCUSSION

1. Preoperative (preemptive) COX-2 inhibitor followed by continued postoperative administration reduced opioid requirements and improved clinical outcomes.
2. Rofecoxib is long-acting (half life = 17 hours) and can be ingested without food by a fasting preoperative patient.
3. Other studies have reported benefits from other forms of preemptive analgesia.
4. COX-2 inhibitors generally do not interfere with platelet and coagulation factors. A small (5% to 10%) potentiation of warfarin effect has been measured in subjects given rofecoxib. Rofecoxib is highly protein bound and may inhibit warfarin binding to plasma protein, resulting in high free warfarin levels and increased INR levels. This study found no significant change in INR or prothrombin time when 50 mg of rofecoxib was co-administered with warfarin. This suggests these pharmacodynamic effects are probably not clinically significant.

5. COX-2 inhibition at the spinal level may be a key factor for efficacy of NSAID administered prior to surgery.

## CONCLUSION

Perioperative (before and after surgery) use of a COX-2 inhibitor was effective component of multimodal analgesia. It reduced opioid consumption, pain, vomiting, and sleep disturbance. It shortened the time physical therapy was needed to achieve effective joint range of motion.

JAMA November 12, 2003; 290: 2411-18 Original investigation, first author Asokumar Buvanendran, Rush-Presbyterian-St Luke's Medical Center, Chicago, IL

Comment:

I wonder if sports medicine enthusiasts might offer pre-game COX-2 inhibitors to players (eg, football) who might be subject to injury during a game. This might lessen the period of disability if a serious injury should occur. RTJ

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## ***“The Optimum Management Of Diastolic Heart Failure Is A Work In Progress.”***

### **11-9 DIASTOLIC HEART FAILURE**

Diastolic heart failure (**DHF**) refers to the clinical syndrome of heart failure (**HF**), with a preserved left ventricular ejection fraction (0.50 and above), in the absence of major valvular disease. About a third of patients with HF seen by clinicians have DHF as so defined.

A simple classification of HF into systolic and diastolic is useful because the two conditions have distinctive pathophysiology and different prognoses.

Doubts regarding DHF have been expressed because the diagnosis of HF is partly a clinical one and prone to error. When left ventricular ejection fraction is low, the diagnosis of HF is seldom questioned.

The advent of biomarkers such as plasma B-type natriuretic peptides should help confirm the presence of HF in patients with suspected DHF.

The evidence base for the diagnosis and treatment of DHF has lagged behind systolic HF. The National Institute of Clinical Excellence in the UK gives token reference to patients with suspected DHF. It suggests that patient with suspected DHF should be “referred for specialist assessment”.

Clinically, patients with DHF are elderly, more likely female, and often have a raised BP and associated left ventricular hypertrophy. However, clinical characteristics by themselves cannot reliably distinguish systolic from diastolic HF. To make the distinction, it is therefore important to obtain an imaging study, typically echocardiography, to estimate left ventricular ejection fraction.

The pathophysiology of DHF is characterized by a *low cardiac output* that results from a ventricle that has thick walls and a small ventricular cavity. (The left ventricular mass/volume ratio is increased.) The left ventricle is stiff. It relaxes slowly early in diastole and offers greater resistance to filling in late diastole. Diastolic pressures are elevated. The low cardiac output manifests as fatigue. The higher end diastolic pressure is transmitted backwards through the valveless pulmonary veins to the pulmonary capillaries resulting in exertional dyspnea.

This triggers neurohormonal activation as in systolic HF. Patients with DHF are unable to augment their stroke volume by increasing their left ventricular end diastolic volume (Frank-Starling mechanism).

Mechanisms contributing to abnormal left ventricular diastolic properties include: stiff large arteries, hypertension, myocardial ischemia, and diabetes.

Acute treatment includes: BP control, relief of ischemia, control of ventricular rate in patients with atrial fibrillation. Chronic treatment includes restriction of dietary sodium, and control of hypertension. But treatment is still largely empirical.

Mortality in DHF is 4 times that of matched controls without HF. The prognosis is generally better than for systolic HF when ambulatory patients are compared, but similar in hospitalized or very elderly patients.

Advances in assessment of left ventricular diastolic function (Doppler imaging) may enhance the ability to identify individuals at high risk of DHF. "Currently, we do not know at what point along the spectrum of diastolic filling abnormalities intervention should be considered necessary to prevent progression of heart failure." "The optimum management of diastolic heart failure is a work in progress."

The best strategy at present to prevent DHF is to achieve better control of high BP and other cardiovascular risk factors.

BMJ November 22, 2003; 327: 1181-82 Editorial by Ramachandran S Vasan, Boston University School of Medicine, Boston, Mass

Comment:

I enjoyed this account. It clarified the concept for me. Current treatment is empirical. Diagnosis is by exclusion of systolic HF. RTJ

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### ***Death Was A Relief To Both Patients And Caregivers***

## **11-10 END-OF-LIFE CARE AND THE EFFECTS OF BEREAVEMENT ON FAMILY CAREGIVERS OF PERSONS WITH DEMENTIA**

More than 6 million adults in the USA provide long-term, unpaid care to disabled elderly family members. This saves the health care system billions. It comes at a price of high levels of distress, increased risk of psychiatric and physical disease, and mortality among family caregivers

Caregivers who care for a family member with dementia face particularly stressful demands owing to the length of the period of care, the behavioral problems associated with dementia, and the extreme impairment of patients with end-stage dementia.

This study describes the caregiving experience of a large cohort of family members who provided in-home care of persons with dementia during the year before the patients' death. It characterized the nature of in-home caregivers' short- and long-term responses to bereavement.

Conclusion: End-of-life care for patients with dementia was extremely demanding. Intervention and support services were needed for most patients before their death. When death was preceded by a protracted and stressful period of caregiving, caregivers reported considerable relief at the death.

## STUDY

1. Assessed type and intensity of care provided by 217 family caregivers (mean age 65; mostly female) of persons with severe dementia (mean age 81) during the year before the patient's death. Assessed caregivers responses to the death.
2. About half the caregivers were spouses. The median time of care was 3 years. Almost all caregivers spent 24 hours per day "on duty" and often stayed in the room of the patient. Half of the caregivers reported spending at least 46 hours a week assisting patients with activities of daily living. Many caregivers who were employed had to reduce hours of work or had to stop working.
3. About half of the caregivers used the services of a home health aide. Many received help from other family members.
4. Over 90% of caregivers believed that death came as a relief to the patients. About 75% reported that the death was a relief to themselves.
5. About 25% of caregivers reported that the patients had been in pain "often" or "all the time".
6. About 20% of caregivers received bereavement services after the patient's death.
7. At the time of death, caregiver's depression scores increased, but within 15 weeks they had declined to a pre-bereavement level. At one year, depression scores were slightly lower. Still, about 30% of caregivers had scores above the level considered to indicate a risk of clinical depression. Scores for depression were significantly higher among caregivers of patients who had been institutionalized.
8. Many caregivers received antidepressant medication and anxiolytics.

## DISCUSSION

1. Family members were intensely involved in providing care for patients with dementia in the last year of the patient's life.
2. Disabled elderly persons wish to remain at home as long as possible and family members want to honor this preference. How can the patient's comfort be maximized, and the caregiver's distress be minimized at the same time?
3. Challenges of care of demented patients include difficulty with communication and pain control, and need for extraordinary vigilance.
4. Caregivers in this study showed remarkable resilience in adapting to the death of their relatives. A large majority reported feeling relieved by the death. Those whose relatives were institutionalized did not however, show as rapid a recovery from depressive symptoms. This suggests that relief from providing daily care alone did not account for the caregivers' recovery from bereavement.
5. Investments in resources for intervention and support may have the largest benefit when they are applied to caregivers and patients in the period that immediately precedes the patient's death. When caregivers know that their relative is on a trajectory toward death, and when they are aware of the patient's disability and suffering, they grieve for the loss of the patient before the death.
6. Clinicians should view bereavement not only as a phenomenon that affects caregivers after the death, but also as one that affects many caregivers before the death occurs.

## CONCLUSION

End-of-life care for patients with dementia is extremely demanding of family caregivers. Intervention and support are needed before the patient's death. Caregivers may report considerable relief at the death.

NEJM November 13, 2003; 349: 1936-42 Original investigation, first author Richard Schultz, University of Pittsburgh, PA.

An editorial in this issue (pp 1891-92) by Holly G Prigerson, Yale University, comments and expands on the study:

The costs of the unpaid, informal care provided by family members have been shown to account for a large proportion of the costs of treating dementia. Although family caregivers spare the health care system billions, illness in the caregivers comes at substantial costs to society. Minimizing depression in caregivers would appear to be an important goal of efforts to reduce the burden of Alzheimer disease on society. The rates of depression in family caregivers of Alzheimer disease patients are higher than among family members who care for other terminal illnesses. The caregivers are typically elderly and may have impaired health. They find themselves in the extraordinary difficult situation of simultaneously providing care and grieving.

Patients with Alzheimer disease live for an average 8 years after the initial diagnosis, and as long as 20 years. The extent and type of care required are particularly demanding, and includes verbal and physical aggression, combativeness, and wandering. End-stage dementia is often *not* recognized as a terminal disease. Patients are less likely to receive palliative services.

Family caregivers undergo the loss of the family member who they knew and loved, and endure the anguish of caring for a loved one who, in many respects is already gone. What makes matters worse is that the patient may appear unappreciative of the enormous sacrifices of their caregiver.

What can the primary care clinician do to help the caregiver?

Try to minimize any physical suffering the patient may experience, and reassure the caregiver that the patient is made as comfortable as possible.

Recognize and treat depression and other illness in caregivers.

Arrange for periodic relief by providing substitute care in the home or temporary institutional care.

Ask for help from Hospice, if available, and request assistance from other community services.

Reassure the caregiver that she is providing loving care and it is appreciated.

Arrange for institutionalization. I believe patients with advanced dementia do not differentiate between their home and a nursing home. They may actually receive better care in a good nursing facility than they would at home. Constant 24-hour care cannot usually be given at home. I would reassure the caregiver and family that institutionalizing the patient is not all bad. RTJ

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*Like Parkinsonism, But Not Parkinsonism*

### **11-11 DEMENTIA WITH LEWY BODIES**

Dementia with Lewy bodies (**DLB**) is one of the 3 most common causes of dementia in older people. Alzheimer's disease and vascular dementia are the other two.

The clinical presentation of DLB typically includes: fluctuating cognitive impairment, visuospatial dysfunction, marked attention deficits, psychiatric symptoms (especially complex visual hallucinations), and mild extrapyramidal features. DLB can usually be differentiated from Parkinson’s disease with dementia because in DLB the motor symptoms usually develop *after* the cognitive impairment. Some authorities require, as a diagnostic criterion for Parkinson’s disease, a delay of at least 12 months between the onset of motor symptoms and subsequent cognitive impairment.

At autopsy 15% to 25% elderly people with dementia have Lewy bodies in the brainstem and cortex.

An accurate antemortem diagnosis is important because patients with DLB are susceptible to severe sensitivity reactions to neuroleptic (antipsychotic) drugs, and because the disease course and prognosis differ from other dementias.

Some patients with DLB may respond to cholinesterase inhibitors.

There is a “need to maintain a high degree of awareness of DLB especially when prescribing neuroleptic drugs for people whose dementia is characterized by early psychiatric symptoms.”

Dementia is a central feature	Core features	Features supporting diagnosis
Progressive cognitive decline sufficient to interfere with social and occupational function.	Fluctuating cognition with pronounced variation in attention and alertness.	Repeated falls
Prominent or persistent memory deficit may not occur in early stages.	Recurrent visual hallucinations typically well formed and detailed.	Syncope
Impairment of attention, and visuospatial ability may be prominent	Spontaneous motor features of parkinsonism	Transient loss of consciousness
		Neuroleptic drug sensitivity
		Systematic delusions
		Non-visual hallucinations.

Lancet November 27, 2003; 362: 1689-90 Editorial by G K Wilcock, Frenchay Hospital, Bristol UK

Comment:

My dictionary defines Lewy body as eosinophilic inclusion body found in the cytoplasm of neurons in the cortex and brain stem in Parkinson’s disease and some forms of dementia. But, as I understand it, DLB is not a form of Parkinsonism, although when dementia occurs in Parkinsonism, the two may be confused. The pathology differs.

Neuroleptic drugs (more simply anti-psychotic drugs) include phenothiazines. (eg, chlorpromazine [*Thorazine*], thioridazine, perphenazine, fluphenazine)

I abstracted this short article to learn more about Lewy dementia. I had not understood much about it.

Still, making the diagnosis does not help the patients much.

RTJ

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***Used Alone Are Equally Effective. Combined Are No More Effective And Cause More Withdrawals***  
**11-12 VALSARTAN, CAPTOPRIL, OR BOTH IN MYOCARDIAL INFARCTION COMPLICATED BY HEART FAILURE, LEFT VENTRICULAR DYSFUNCTION, OR BOTH**

Angiotensin-converting-enzyme inhibitors (**ACE-I**) do not completely block production and effects of angiotensin II. Likewise, angiotensin-receptor blockers (**ARB**) do not completely block angiotensin II. But, they

do act differently. Investigators have speculated that adding the two would produce greater benefits than either one used alone.

This study tested whether an ARB (*valsartan*) alone, or an ACE inhibitor (*captopril*) alone, or the two combined would produce the most benefits in patients at high risk after MI.

Conclusion: Valsartan alone, and captopril alone were equally effective. The combination was no more effective and caused more adverse effects.

## STUDY

1. Entered over 14 500 patients (mean age 65) within 1 to 10 days after an acute MI that was complicated by clinical or radiological signs of HF, evidence of left ventricular systolic dysfunction, or both.
2. Randomized to: 1) valsartan alone, 2) captopril alone, or 3) the two combined.
3. All other drugs used by patients were continued.
4. Primary end-point = death from any cause.
5. Follow-up = 2 years.

## RESULTS

- |  |           |           |  |
|--|-----------|-----------|--|
| 1. At 2 years  | Valsartan | Captopril | Both   |
| Total Deaths   | 19.6%     | 19.6%     | 19.3%  |
| 2. Any adverse event   | 29%       | 28%       | 35% (leading to dose reduction or discontinuation) |
| 3. Myocardial infarction (fatal and non-fatal), heart failure (fatal and non-fatal), and stroke were essentially the same in all 3 groups (no statistical difference). |           |           |  |

## DISCUSSION

1. International guidelines recommend ACE-I as first-line therapy for patients at high risk such as those with HF or left ventricular dysfunction after a MI. Captopril, ramipril, and trandolapril have all been shown to be superior to placebo, resulting in a 26% reduction in mortality.
2. This study found that the ARB valsartan was just as effective (but not more effective) as the ACE inhibitor captopril in improving survival and reducing cardiovascular morbidity.
3. Combining the two drugs did not add any benefit in reducing mortality or morbidity despite additional lowering of BP. The combination produced a clear increase in the rate of intolerance. This is in contrast to two other recent trials of patients with HF which reported that an ARB provided improvements in cardiovascular outcomes when added to patients receiving an ACE inhibitor.
4. Given that valsartan was just as effective as captopril makes it a clinically effective alternative therapy.

## CONCLUSION

Valsartan is as effective as captopril (but not more effective) as measured by risk of death in patients who are at high risk for cardiovascular events after a myocardial infarction. The combination increased adverse effects without improving survival.

NEJM November 13, 2003; 349: 1893-906 Original investigation by the Valsartan in Acute Myocardial Infarction Trial Investigators (VALIANT), first author Marc A Pfeffer, Brigham and Women's Hospital, Boston Mass.

Comment:

I abstracted this study because it contrasts with other studies reported in *Practical Pointers*. Doubt remains about the efficacy of combined ACE inhibitors and ARBs. See "Effects of Candesartan on Mortality and Morbidity in Patients with Chronic Heart Failure" *Practical Pointers* September 2003. The study reported a slight benefit when candesartan was added to ACE inhibitors. (NNT = 25 to 50) Hyperkalemia, hypotension, and increased creatinine levels occurred more commonly in the combined group.

I believe primary care clinicians should avoid the combination until clarification is available. ARB may be used when ACE inhibitors are not tolerated. RTJ

There is a considerable cost differential at the final doses suggested:

Valsartan (*Diovan*) \$1.63 for one day

Captopril (*Generic*) \$0.60 for one day