

PRACTICAL POINTERS
FOR
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JUNE 2007

ANTIHYPERTENSION THERAPY IMPROVES DIASTOLIC FUNCTION

ESTROGEN-ALONE THERAPY MAY HAVE CARDIOPROTECTIVE EFFECTS. IN YOUNGER WOMEN

THE IMPORTANCE TO TIMING IN PRESCRIBING HORMONE REPLACEMENT THERAPY

SOCIAL DISTANCING TO CONTROL FLU EPIDEMIC

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DOES FOLIC ACID SUPPLEMENTATION REDUCE RISK OF STROKE?

CARDIAC RESYNCHRONIZATION FOR LEFT VENTRICULAR DYSFUNCTION

HOW SHOULD YOU INTRODUCE YOURSELF WHEN FIRST MEETING A PATIENT?

A REMARKABLE NEW THERAPY FOR STRESS INCONTINENCE.

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of Practical Pointers.

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.

Editor/Publisher.

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HIGHLIGHTS AND EDITORIAL COMMENTS JUNE 2007

Diastolic Function Was Improved In Both Groups

6-1 EFFECT OF ANGIOTENSIN RECEPTOR BLOCKADE AND ANTIHYPERTENSIVE DRUGS ON DIASTOLIC FUNCTION IN PATIENTS WITH HYPERTENSION AND DIASTOLIC DYSFUNCTION:

Diastolic dysfunction is characterized by impaired ventricular relaxation and abnormalities of ventricular filling. It is an important pathophysiological intermediate between hypertension and heart failure (HF), especially HF with normal systolic ejection fraction.

This study aimed to determine whether lowering BP with an angiotensin II receptor blocker would improve diastolic function to a greater extent than would non-renin-angiotensin-aldosterone system (RAAS) pharmacological approaches.

Double-blind, randomized, placebo-controlled trial entered 384 patients mean age 61. All had a history of stage 1 or stage 2 hypertension. All had systolic ejection fractions over 50%.

Patients were randomized to: 1) Valsartan (*Diovan*; Novartis) 160 mg once daily titrated up to 320 mg once daily in addition to standard antihypertension therapy, or 2) Placebo in addition to standard antihypertension therapy (diuretics, beta-blockers, calcium blockers, and alpha blockers). The goal was to achieve a BP < 135/80 in both groups.

Determined the lateral mitral annular relaxation velocity by doppler echocardiography.

Patients were included in the study on the basis of velocities lower than age-specific cutoff values.

Outcomes (means)	Baseline		38 weeks	
	Valsartan	Placebo	Valsartan	Placebo
Systolic BP	144	141	131	135
Diastolic BP	86	87	79	82

Compared with baseline, increases in relaxation velocities were observed at 38 weeks in both groups. (But no significant difference between groups)

There were reductions from baseline to follow-up in isovolumetric relaxation time, ventricular wall thickness, left ventricular mass, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left atrial volume; and an increase in ejection fraction in both groups.

Diastolic dysfunction represents a central abnormality in patients with HF. It is characterized by delayed relaxation, slowed and incomplete filling of the left ventricle, and decreased distensibility of the left ventricle. (An upward shift in the relation between end-diastolic pressure and left ventricular volume. A greater diastolic pressure is required to fill the left ventricle to the same volume.)

Conclusion: Lowering BP improved diastolic function irrespective of the type of anti-hypertension agent used.

It has long been appreciated that diastolic function is impaired in many patients with HF while systolic ejection fractions remain normal (over 50%). Diastolic function has been difficult to measure. Fortunately, more precise measurements are becoming available. This study is an important addition to the pathophysiology of HF. Diastolic dysfunction can occur at relatively low stages of hypertension and at a relatively young age.

As we age, our ventricles become stiffer, especially if we have increases in BP, even modest increases. Note the baseline mean BP was 144/86. This degree of hypertension may not be treated in primary care practice, particularly in elderly patients. It is becoming evident that treating even this modest degree of hypertension will bring benefits. Treat BP early and vigorously, including stage 1 hypertension. This will reduce the incidence of HF.

These investigators tilt toward use of RAAS inhibition (an angiotensin II blocker in preference to an ACE inhibitor) in addition to other drugs as needed.

Deciding to treat modest elevations of BP in the elderly is more difficult than in younger patients. Adverse effects of anti-hypertension drugs are more frequent as kidney and liver function declines, and elimination of drugs is impaired. Adverse effects are more disturbing in older persons. Treat them gently and gradually. I believe even a modest decrease in BP will improve diastolic function.

“Estrogen Therapy May Have Cardioprotective Effects In Younger Women.”

6-2 ESTROGEN THERAPY AND CORONARY-ARTERY CALCIFICATION: The WHI-CACS Trial

This **WHI-CACS** study determined whether the coronary-artery calcium burden differed (after 7 years of therapy) among women age 50 to 59 at baseline who received estrogen-alone vs those who received placebo.

The study was restricted to women age 50-59 (mean = 55) at randomization. This is the most clinically relevant age group with regard to initiation of CEE for menopausal symptoms.

Between May and September 2005, 1079 women underwent CT examinations of the heart. At that time, subjects' mean age was 65 years. They had taken CEE or placebo for an average of 7 years.

Mean calcium score:	CEE (n = 547)	Placebo (n = 527)
	83	123

“Estrogen therapy may have cardioprotective effects in younger women.” But, estrogen has complex biological effects that may vary according to the underlying state of the vasculature. It is possible that estrogen could reduce coronary artery calcium scores but still increase the risk of clinical CHD events, owing to adverse effects on thrombosis and plaque rupture, which are more likely in older women.

Conclusion: Among women age 50-59 estrogen at baseline, estrogen-alone given for 7 years was associated with a lower coronary artery calcium burden than those who received placebo.

This should reassure women who have recently undergone menopause and need relief of symptoms.

Coronary calcium is, of course, a surrogate outcome for coronary events. The investigators did not mention rate of clinical events. I presume there were few in this age group.

Women who had hysterectomy, and thus can take estrogen-alone for menopausal symptoms, are in the minority. The larger problem concerns those who require combined estrogen-progesterone. I believe combined E + P is associated with more adverse effects (stroke, breast cancer, and CHD events) than E-alone. Nevertheless, E + P is reasonably safe, and safer in younger postmenopausal women than in older women.

E-alone is not entirely safe. It is associated with increased risk of stroke and venous thromboembolism.

I believe that women who have no traditional risk factors and who take hormones at any time post-menopause are less likely to be at risk for adverse effects than women who have a number of traditional risk factors and do not take hormones.

Another study by the WHI “Effects of Conjugated Estrogens on Breast Cancer” JAMA April 12,2006 (See Practical Pointers April 2006 [4-9] provides some reassurance about the risk of breast cancer in postmenopausal women taking estrogen-alone therapy. Over 10 000 women, the majority over age 60, were randomized to CEE or placebo and followed for 7 years. There was no increase in incidence of breast cancer in the CEE group. .

I believe progesterone is the main hormonal risk factor for breast cancer.

The Importance Of Timing

6-3 HRT AND THE YOUNG AT HEART

Clarity about hormone-replacement therapy (**HRT**) is emerging. Its effects differ according to the age of the recipient. This underscores the importance of timing. The WHI-CACS and other WHI studies support the “timing hypothesis” for HRT. HRT is related to more adverse cardiovascular effects in older women. As women age, the underlying biological characteristics of the vessel wall and the vascular response to HRT change.

The WHI-CACS supports recent consensus statements of two large societies of menopause practitioners which strongly endorse the timing hypothesis and recognize the potentially beneficial effects of HRT in younger postmenopausal women.

It is important to continue to emphasize that HRT should not be considered as a strategy to *prevent* CVD in women. There are proven therapies for prevention that remain underused.

The editorialists go on to describe the recent history of recommendations for HRT. (*See the full abstract.*) The perceived safety and recommendations for use of HRT have varied over the past decades, and have led to confusion among patients and physicians alike.

A clearer consensus is now evolving. HRT in younger postmenopausal women is safe.

I enjoyed reviewing the conflicting reports about post-menopausal hormone therapy. The best guidelines of “evidence-based-medicine” can vary over the years. No wonder women and their physicians were confused.

The term “hormone replacement therapy” (HRT) is confusing, and I believe should be abandoned. There is a great clinical difference between estrogen-alone, progesterone-alone, and both combined. Perhaps post-menopausal xxx therapy (xxx specifying the hormone used) would be a better term.

Back To Basics

6-4 SOCIAL MEASURES MAY CONTROL PANDEMIC FLU A Message from a Recent Conference In Barcelona

Non-pharmacological interventions may be as important as, or even more important than, drugs and vaccines in fighting pandemic flu.

“Social distancing” will be important to help reduce the numbers of cases and also to slow the spread of the epidemic, buying time for production of a vaccine.

I believe “old-fashioned” prophylaxis and hygienic methods are indeed effective, but oft forgotten. “Ring prophylaxis”—isolating and treating the patient while using prophylaxis for those closely associated—is also a necessary intervention to control epidemics. Individuals must be responsible for their own “social isolation”.

“Gonococcus is an incredible bug because it adapts incredibly quickly.”

6-5 GONOCOCCAL INFECTIONS

Update from the CDC:

Fluoroquinolones no longer recommended

See the full abstract for the current CDC recommendations.

Lancet May 12, 2007; 369: 1592 “World Report”, by Michael McCarthy, Lancet Staff. comments:

“Gonococcus is an incredible bug because it adapts incredibly quickly.”

Cephalosporins now remain the last class of antibiotic for which important resistance has not been detected.

“Emergence of strains resistant to cephalosporins is only a matter of time.”

“We Should Not Delay In Allowing Snus To Compete With Cigarettes.”

6-6 SNUS—What should the public health response be?

In most developed countries, about a fifth of annual deaths are caused by smoking. Many people have a serious smoking-caused illness each year, the most being respiratory diseases.

Snus, a form of smokeless tobacco, has lower levels of toxins than most other smokeless tobaccos. Snus has been estimated to be 90% less harmful than cigarettes. It has become the dominant form of tobacco used by Swedish men, who now have an unusually low smoking rate.

It is banned in countries in the European Union other than Sweden.

A study from Sweden now reports that oral cancer and lung cancer are *not* increased in snus users compared with never-users. A study from Australia, where snus is also banned, estimates that snus could produce a net health benefit, dependent on how many inveterate smokers would switch to snus.

Snus is not harmless. It can cause gingival recession and adverse outcomes in pregnancy. There is conflicting evidence about cardiovascular risks. However, for all the major smoking-related diseases, the risks are lower with snus than with smoking. Importantly, snus poses *no risk* for lung cancer and chronic obstructive pulmonary disease.

“We believe it is preferable that, if people become addicted to cigarettes or decide to try tobacco, they can use a product that is markedly less harmful than cigarettes.” In Sweden, primary use of snus is associated with reduced risk of cigarette smoking. “We should not delay in allowing snus to compete with cigarettes.” “We should be prepared to accurately inform smokers about the relative risks of cigarettes, snus, and approved smoking-cessation medications.”

I repeatedly said to myself “Amen” while abstracting this article.

All drugs are harmful (no exceptions). This includes the now available drugs marketed for smoking cessation. We accept the possible harm of all drugs to gain a much greater perceived benefit.

I would welcome a head-to-head comparison of snus with the now available nicotine replacement therapies in smokers who wish to quit. How would the benefit / harm-cost ratios compare? Which one would be more acceptable to patients and be more likely to lead to persistent cessation of smoking? If snus were a drug manufactured by “Big Pharma”, I believe it would be FDA approved, widely advertised, and made universally available as a nicotine-based aid to cessation.

If snus were available in the US, I would not hesitate to advise it as an aid to smoking cessation after advising the patient about its possible harms, and offering information about comparable risks and benefits of snus vs other available aids to cessation. Indeed, if a smoker has tried a number of times to quit, I would advise use of snus as another attempt. Snus might be a bridge for smokers to use to gradually taper nicotine dependence.

Snus is not the same as snuff available in the US market. It is less toxic.

Communication Into One Manageable Channel.

6-7 COMMUNICATION BETWEEN PHYSICIANS AND PATIENTS IN THE ERA OF E-MEDICINE

Clinics are beginning to invite patients to use a secure Internet link to communicate with physicians and staff members. The field is evolving swiftly. Web messaging is an attempt to direct round-the-clock communication into one manageable channel.

E-medicine could comprise 4 major types of services: 1) online appointment scheduling, 2) electronic prescription refills, 3) general messaging capabilities, and 4) “Web visits” with physicians. General messages permit patients to ask simple questions, obviating many telephone calls. “Web visits” are structured consultations focused on non-urgent chief complaints involving menus of questions tailored to the problem, brief answers by the patient, and a response from the physician within a certain period.

E-medicine may also enable hospitals to improve transitions of care of patients.

The federal government has set out a National Information Technology plan with a goal of establishing electronic health records systems for most Americans by 2014.

What do doctors think? Many appreciate the asynchronous nature of Web messaging. Patients contact doctors at their convenience. Physicians respond when they have a moment. Most physicians find it much easier to respond to queries in this form than to return phone calls.

The emerging model will improve the practice of medicine, but will also bring new challenges.

“The ‘laying on of hands’ will increasingly include the ‘pressing of keys’.

Physician-patient communication has been at times a weak link in the relationship. Patients remain anxious waiting for a report of a biopsy or lab result. E-medicine may facilitate more timely reporting.

I would regret the loss of “laying on of hands”. Our world is becoming less personal. Machines are replacing the human voice. Is it your doctor responding, someone who does not know you, or even a machine?

But, I believe, ready or not, in the name of efficiency, the brave new world is coming. Get ready!

“Our Findings Remain To Be Confirmed.”

6-8 EFFICACY OF FOLIC ACID SUPPLEMENTATION IN STROKE PREVENTION: A meta-analysis

Initial epidemiological evidence supported the hypothesis linking elevated homocysteine levels with increased risk of coronary artery disease, stroke, and deep vein thrombosis; and that treatment with folic acid reduced risk.

Randomized trials have reported inconsistent results, and have not supported the hypothesis that lowering homocysteine reduces risks. Most of these trials have been conducted in patients with established cardiovascular disease. It is possible that folic acid supplementation could have a greater protective effect in primary rather than in secondary prevention; and that different cardiovascular endpoints could respond differently to folic acid.

This meta-analysis focused on stroke as the disease endpoint in relation to folic acid supplementation.

Collected data from 8 randomized trials (over 16 500 individuals, most over age 60) of folic acid (with or without B6 and B12) supplementation vs placebo. All reported stroke as one of the endpoints. All trials included individuals with pre-existing cardiovascular or renal conditions.

Pooling results of all trials indicated a statistically significant reduced risk of stroke in the folic acid treatment groups. (Relative risk [RR] = 0.82; folic acid vs placebo). Longer-duration trials were associated with greater benefit in reducing stroke. Less than 36 months RR = 1.0; longer than 36 months RR = 0.71. In the one study of subjects with a history of stroke, the RR was 1.04 vs a RR of 0.75 in 7 studies of subjects without a history of stroke (but with other vascular diseases).

“Our meta-analysis provides coherent evidence that folic acid supplementation can significantly reduce the risk of stroke in primary prevention.”.

There is continued controversy with regard to whether folic acid can lead to improved outcomes for other cardiovascular endpoints. Several randomized trials of folic acid supplementation have in general yielded negative results. However, different endpoints (eg stroke vs other cardiovascular endpoints) could respond differently.

“Our findings remain to be confirmed.”

Conclusion: “Our findings indicate that folic acid supplementation can effectively reduce the risk of stroke in primary prevention.”

The homocysteine-folic acid controversy seems to have 9-cat-lives.

This meta-analysis was not really an analysis of “primary” prevention. At baseline, all subjects had established atherosclerotic disease. In a truly “primary” prevention trial all subjects at baseline should be free of atherosclerotic disease.

It would take a long time and a large trial of folic acid supplementation vs placebo in subjects without any atherosclerotic vascular disease at baseline to determine any benefit.

This meta-analysis does not convince me. What would be the reason to consider that stroke (a vascular disease) differs from other vascular diseases?

How should primary care clinicians respond to the presently available information?

I believe it reasonable, since doubt remains, to offer supplementation. The benefit / harm-cost ratio of folic acid may be high because the harm-cost is so low.

Moderate Effectiveness In Clinical Practice

6-9 CARDIAC RESYNCHRONIZATION THERAPY FOR PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION: A Systematic Review

Despite many advances, for many patients with heart failure (**HF**), morbidity and mortality remains high, and quality-of-life is poor. “Thus, there is increasing enthusiasm for the therapeutic potential of atrial-synchronized biventricular pacemakers (cardiac resynchronization therapy; **CRT**) in patients with heart failure and left ventricular (**LV**) systolic dysfunction.”

About 1% to 3% of all patients discharged alive after their initial hospitalization for HF meet CRT trial criteria:

LVEF < 35%

QRS > 120 milliseconds

Sinus rhythm

NYHA class 3 or 4 despite optimal medical therapy

This review summarizes the current evidence regarding the efficacy (outcomes in randomized trials) and effectiveness (outcomes in clinical settings), and safety of CRT in patients with LV systolic dysfunction. In randomized, controlled trials, 59% of CRT recipients improved at least one NYHA class vs 37% of controls. Compared with controls, left ventricular ejection fraction increased by 3%; 6-minute walk test distance increased by 24 meters; and quality-of-life increased by 8 points on a living with heart failure questionnaire. Hospitalizations for HF were less frequent in the CRT subjects (19% vs 27%). All cause mortality 13% vs 15%.

. Safety: Implantation success = 93%; peri-implantation mechanical complications 4%; peri-implantation deaths 0.3%; 5% malfunctioned within 6 months; 2% hospitalized for infections in the implant site; lead problems in 7%.

Conclusion: CRT is efficacious in clinical practice, and is cost-effective therapy for patients with class 3 or 4 HF (despite optimal medical management), and a LVEF less than 35%, sinus rhythm, ventricular dyssynchrony (currently identified by a prolonged QRS duration).

Primary care clinicians should know about this intervention, and be able to inform suitable patients about its availability. Some patients may be interested. To me, the increase in quality of life would be the most attractive outcome.

But, take care in referral! The track record of the reference cardiology group must be known. I would not rely on this report to judge adverse effects.

“Can Set A Positive Tone

6-10 AN EVIDENCE-BASED PERSPECTIVE ON GREETINGS IN MEDICAL ENCOUNTERS

The purpose of this study was to provide some guidance by defining patient-expectations for physician behavior during the greeting stage of the initial medical visit.

Conducted a cross-sectional random telephone survey of adults (ie, patients) in the US. (415 persons responded.) Asked closed-ended questions about their preferences for shaking hands, use of patients' names, and use of physicians' names, especially at the first meeting.

The majority of patients preferred the doctor to shake hands. A surprising number wished to be addressed by their first names. Most wanted the doctors to introduce themselves with their first and last names.

“While greetings may seem a rather mundane aspect of physician-patient communication, attention to this task can set a positive tone for the encounter, and increase the chances of developing a therapeutic clinical relationship.”

Conclusion: Physicians should be encouraged to shake hands, and initially use patient's first and last names, and introduce themselves with their own first and last names.

This would seem a self-evident courtesy to someone as old as I am. The younger generation may differ. I know that some elders bristle when a young doctor calls them by their first name before they develop a closer relationship.

Although this may seem old-fashioned to some, I believe it common courtesy, when encountering another person (or when calling on the telephone) to first say “good morning”, “good afternoon”, or “good evening” before launching into the purpose or question of the encounter. This recognizes the individual first, and only secondarily as a source of information.

A Remarkable Pioneering Technique Which May Provide Comfort To Many Women

6-11 AUTOLOGOUS MYOBLASTS AND FIBROBLASTS VERSUS COLLAGEN FOR TREATMENT OF STRESS URINARY INCONTINENCE IN WOMEN

A new technique for treatment of stress incontinence involved taking a muscle biopsy, processing the tissue, and placing it in tissue culture flasks to grow myocytes and fibrocytes. The autologous cells were injected into the urethra by guidance with a special ultrasound.

Of 42 women, 38 obtained complete continence. There were no adverse effects.

Read the full abstract. This is a pioneering application. Although not applicable to primary care, I could not resist abstracting the article. More observation is obviously needed before the technique can be applied generally. If it is perfected and becomes generally available, it has the potential to provide comfort to millions of women.

ABSTRACTS JUNE 2007

Diastolic Function Was Improved In Both Groups

6-1 EFFECT OF ANGIOTENSIN RECEPTOR BLOCKADE AND ANTIHYPERTENSIVE DRUGS ON DIASTOLIC FUNCTION IN PATIENTS WITH HYPERTENSION AND DIASTOLIC DYSFUNCTION: A Randomized Trial.

Patients with hypertension are at increased risk of left ventricular hypertrophy (**LVH**), myocardial fibrosis, and chronic heart failure (**HF**).

Diastolic dysfunction is characterized by impaired ventricular relaxation and abnormalities of ventricular filling. This is an important pathophysiological intermediate between hypertension and HF, especially HF with normal systolic ejection fraction.

To date, no specific treatments have been shown definitively to improve diastolic function.

Long-term treatment of hypertension results in regression of existing LVH.

Determining the effect of treatment on diastolic function has been limited by difficulties in assessing diastolic function non-invasively. Recent advances in doppler echocardiography have allowed direct measurement of myocardial relaxation velocities, a robust non-invasive measure of diastolic function.

This study aimed to determine whether lowering BP with an angiotensin II receptor blocker would improve diastolic function to a greater extent than would non-renin-angiotensin-aldosterone system (**RAAS**) pharmacological approaches.

Conclusion: Lowering BP improved diastolic function irrespective of the type of antihypertensive agent used. The angiotensin II blocker did not confer greater benefit than other drugs.

STUDY

1. Double-blind, randomized, placebo-controlled multicenter trial entered 384 patients mean age 61. All had a history of stage 1 or stage 2 hypertension, treated or untreated. None had stage 3 hypertension. (BP > 180/110). None had a history of admission for HF within the past year.
2. All underwent echocardiographic screening for systolic and diastolic function. All had a systolic ejection fraction of over 50%. All had diastolic dysfunction. LVH was present in only 3%.
3. The lateral mitral annular relaxation velocity was determined by doppler echocardiography. Patients were included in the study on the basis of ventricular relaxation velocities lower than age-specific cutoff values.
4. Patients were randomized double-blind to: 1) Valsartan (*Diovan*; Novartis) 160 mg once daily titrated up to 320 mg once daily in addition to other standard antihypertension therapy, or 2) Placebo in addition to standard antihypertension therapy (diuretics, beta-blockers, calcium blockers, and alpha blockers).
5. The goal was to achieve a BP < 135/80 in both groups.
6. Primary outcome measure = change in diastolic myocardial relaxation velocity from baseline to 38 weeks.

RESULTS

1. At baseline, the mean lateral mitral relaxation velocity in all patients was substantially reduced compared with

historical controls. It was inversely related to age.

2. Outcomes (means)	Baseline		38 weeks	
	Valsartan	Placebo	Valsartan	Placebo
Systolic BP	144	141	131	135
Diastolic BP	86	87	79	82

(Slightly greater reduction in valsartan group.)

3. Increases in relaxation velocities were observed at 38 weeks in both groups compared with baseline.

There was no significant difference between treatment groups.

4. There were reductions from baseline to follow-up in isovolumetric relaxation time, ventricular wall thickness, left ventricular mass, left ventricular end-diastolic volume, left ventricular end-systolic volume, and left atrial volume; and an increase in ejection fraction in both groups.

DISCUSSION

1. Reduction in BP was associated with improvement in diastolic function in patients with hypertension

irrespective of whether BP lowering was achieved by an RAAS inhibitor or other antihypertension therapy.

2. Diastolic dysfunction could represent an early measure of myocardial end-organ damage in hypertension that might precede ventricular hypertrophy. This suggests a potential mechanism by which treating hypertension might attenuate progression to heart failure.

3. Diastolic dysfunction represents a central abnormality in patients with HF. It is characterized by delayed relaxation, slowed and incomplete filling of the left ventricle, and decreased distensibility of the left ventricle. (An upward shift in the relation between end-diastolic pressure and left ventricular volume. A greater diastolic pressure is required to fill the left ventricle to the same volume.)

4. Diastolic dysfunction can be present in hypertensive patients without overt LVH, and might represent an early marker of end-organ damage. Diastolic abnormalities precede LVH.

5 Up to 15% of persons age 65 years or older with doppler evidence of diastolic dysfunction, but without HF, have an estimate risk of developing HF within 5 years.

6 The prevalence of diastolic dysfunction in patients with a history of treated or untreated hypertension is high. Up to 50% of patients with a history of hypertension have evidence of diastolic dysfunction.

7. Inhibition of RAAS offers health benefits beyond BP reduction. RAAS inhibitors are associated with greater regression of LVH than other anti-hypertension drugs, including diuretics, beta-blockers, and calcium blockers. RAAS inhibitors also improve myocardial fibrosis in association with improvement in parameters of diastolic function. Two outcome studies have reported benefits of RAAS in reducing hospitalization for HF and preserving ejection fractions.

8. Load reduction could have a role in the observed improvement in diastolic function. Increases in afterload (blood pressure) cause a decrease in early diastolic filling and in myocardial lengthening.

9. The patients in this study were young, mildly hypertensive and without HF. However, it is likely that patients

with even more severe hypertension would show improvements in diastolic function as BP is lowered. The greatest improvement in diastolic function noted in this study occurred in individuals with the greatest reduction in BP.

CONCLUSION

Lowering BP improved diastolic function irrespective of the type of anti-hypertension agent used.

Lancet June 23, 2007; 369: 2079-87 Original investigation by the Valsartan in Diastolic Dysfunction (VALIDD) investigators, first author Scott D Solomon, Brigham and Women's Hospital, Boston Mass. Study supported by Novartis.

“Estrogen Therapy May Have Cardioprotective Effects In Younger Women.”

6-2 ESTROGEN THERAPY AND CORONARY-ARTERY CALCIFICATION: The WHI-CACS Trial

Recent randomized clinical trials have cast doubt on a cardioprotective role of exogenous estrogen. The Women's Health Initiative (WHI) trial of conjugated equine estrogens (CEE; *Premarin*; Wyeth 0.625 mg daily vs placebo) in postmenopausal women (mean age 64 at baseline) who had undergone hysterectomy, reported that protection against non-fatal myocardial infarction (MI) and fatal coronary heart disease (CHD), compared with placebo, varied with the age of the recipient:

Age	Hazard ratio CEE vs placebo
50-59	0.63
60-69	0.94
70-79	1.11

Estrogen was also related to a reduced risk of a need for coronary revascularization in younger women.

The findings in younger women were consistent with previous observational studies which included women who initiated estrogen therapy early in the menopause.

This WHI-CACS study determined whether the coronary-artery calcium burden differed (after 7 years of therapy) among women age 50 to 59 at baseline who received estrogen-alone vs those who received placebo.

Conclusion: Among women age 50-59 estrogen at baseline, estrogen-alone given for 7 years was associated with a lower coronary artery calcium burden than those who received placebo.

STUDY

1. The WHI trial¹ which randomized hysterectomized women (mean age 64 at randomization) to CEE or placebo, was stopped early because of an increased risk of stroke in the CEE group, without any apparent benefit on CHD. (There was a suggestion of a reduced risk of CHD in age group 50-59, but not statistically significant.)
2. The present study, termed the WHI-CACS study, is an ancillary study to explore the effect of CEE on coronary calcification in younger postmenopausal women as a marker of atherosclerotic CHD.

3. The WHI-CACS was restricted to women age 50-59 (mean = 55) at randomization in the WHI trial. This is the most clinically relevant age group with regard to initiation of CEE for menopausal symptoms.
4. Between May and September 2005, 1079 women underwent CT examinations of the heart. At that time, subjects' mean age was 65 years. They had taken CEE or placebo for an average of 7 years.
5. Coronary artery calcium scores were grouped:

0	no calcification
1 to 9	minimal
10 to 100	mild
101 to 300	moderate
Over 300	extensive

RESULTS

1. Cardiovascular risk factors were similar between women who received CEE and those who received placebo.
2. Mean calcium score:

CEE (n = 547)	Placebo (n = 527)
83	123
3. The 50th, 60th, 75th and 95th percentiles values of coronary artery calcium scores:

CEE	0	3	43	452
Placebo	0	17	84	689
4. When analyses were restricted to women who had taken CEE at least 80% of the time for 5 years, calcium scores were lower than in the entire cohort taking CEE.
5. Past or current smoking, hypertension, high cholesterol, and diabetes were strongly predictive of elevated coronary artery calcium scores. These factors did not significantly alter the relationship between treatment with CEE and calcium scores.

DISCUSSION

1. Atherosclerotic calcification of the coronary arteries is a subcomponent of atherosclerotic plaques, and a marker of the total plaque burden in the coronary arteries. Vascular deposits of calcium develop as part of the chronic inflammatory process of atherosclerosis. Computed tomography of the coronary arteries can detect and quantify the calcium burden. Coronary artery calcification has been shown to be predictive of future cardiovascular events, independently of traditional risk factors.² In a large cross-sectional study, the risk of CHD increased by a factor of 30 from the lowest to the highest quartile of coronary artery scores.
2. In this study, calcium scores were also strongly associated with traditional risk factors for CAD, providing support for the role of this measure as a marker of atherosclerosis.³
3. This WHI-CACS trial assessed the post-trial burden of calcified atheroma in the coronary arteries in women age 50-59 at randomization to CEE or placebo into the WHI trial.
4. At an average of 9 years after the original randomization, women receiving CEE had a lower prevalence and

quantity of coronary-artery calcium than those receiving placebo.

5. Among women assigned to CEE, those who were more compliant with taking CEE over 5 years or more, had lower levels of coronary artery calcium as compared with the entire cohort taking CEE.
6. “These findings, in conjunction with the suggestion of a reduced risk of clinical coronary events among women treated with conjugated equine estrogens in this age group, are consistent with previous evidence from laboratory, animal, and observational studies.”
7. “Estrogen therapy may have cardioprotective effects in younger women.” But, estrogen has complex biological effects that may vary according to the underlying state of the vasculature. It is possible that estrogen could reduce coronary artery calcium scores but still increase the risk of clinical CHD events, owing to adverse effects on thrombosis and plaque rupture, which are more likely in older women.

CONCLUSION

Among women age 50-59 at baseline, the calcified-plaque burden in the coronary arteries was lower in women assigned to CEE vs those assigned to placebo.

Estrogen, given alone, is unlikely to have an adverse effect on the risk of coronary events among women who have recently undergone menopause. Hormone therapy should be limited to the treatment of moderate-to-severe menopausal symptoms with the lowest dose for the shortest time.

NEJM June 21, 2007; 356: 2691-2602 Original investigation by the WHI and WHI-CACS Investigators, first author JoAnn E Manson, Brigham and Women’s Hospital and Harvard Medical School, Boston , Mass.

1 JAMA 2004; 291: 1701-12 “Effect of Conjugated Equine Estrogen in Postmenopausal Women with Hysterectomy” (See Practical Pointers April 2004 [4-4])

2 This begs the question—should primary care clinicians advise their patients to undergo CT screening for coronary calcification as a risk marker? I would advise against this because it would not lead to any interventions to reduce risks of coronary events in addition to those determined by traditional risk factors.. We already have an abundance of risk markers on which to act. (Note the number of risk factors present in subjects in the WHI study.) Adding determination of the calcium burden in the arteries would not lead to any additional recommendations to reduce risk (ie, to treat dyslipidemia, control hypertension, control blood glucose, control BMI and waist circumference, avoid a sedentary lifestyle, control dietary intake of saturated and trans fats, reduce intake of high glucose loads).

3 At baseline, 12% were smokers, 35% had hypertension, 10% had high cholesterol, 6% diabetes.

The Importance Of Timing

6-3 HRT AND THE YOUNG AT HEART

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

Clarity about hormone-replacement therapy (**HRT**) is emerging. Its effects differ according to the age of the recipient. This underscores the importance of timing. The WHI-CACS and other WHI studies support the “timing

hypothesis” for HRT. HRT is related to more adverse cardiovascular effects in older women. As women age, the underlying biological characteristics of the vessel wall and the vascular response to HRT change.

The WHI-CACS supports recent consensus statements of two large societies of menopause practitioners which strongly endorse the timing hypothesis and recognize the potentially beneficial effects of HRT in younger postmenopausal women.

It is important to continue to emphasize that HRT should not be considered as a strategy to *prevent* CVD in women. There are proven therapies for prevention that remain underused.

The editorialists review several WHI trials reported over the years. [*Practical Pointers* has abstracted these articles. I combine the remarks from both sources RTJ.]

1. For a number of years, some epidemiological studies suggested a protective effect of HRT against coronary heart disease (CHD). This was based on reasonable physiological considerations. It was theorized that CHD becomes more common in women after the menopause because a protective effect of estrogen wears off. In addition, estrogen has beneficial effect on serum lipids. In retrospect, data were biased by “the healthy user effect”.

2. In 2002, The WHI reported a large 5-year trial of CEE + medroxyprogesterone (E + P vs placebo) in women mean age 63 at baseline. In the HRT groups there was a slight *excess* of CHD events (death, non-fatal MI, stroke, pulmonary embolus, invasive breast cancer). The main conclusion was that HRT did not benefit in prevention of chronic disease, and indeed may be harmful. This caused widespread concern in women who were taking HRT. Many stopped taking it, and suffered an increase in discomforting menopausal symptoms. (*Practical Pointers* July 2002 [7-3])

3. In 2003, a trial reported that CEE + progesterone *increased* the number of cardiovascular events in a large group of women age 50 to 79 (mean age 63). This raised concerns about its overall safety. HRT did not have the cardiovascular benefits expected. This caused widespread confusion and debate. (*Practical Pointers* August 2003 [8-2])

4. In 2004, the WHI estrogen-only trial (WHI-CEE) was reported, again in women age 50 to 79. Overall, women showed *no increase* in the incidence of CHD. Results suggested a potential *benefit* of estrogen on heart disease in women age 50-59. The study reported an increase in risk of stroke and was terminated prematurely. (*Practical Pointers* April 2004 [4-4])

Hazard ratios of CEE vs placebo in this study were:

CHD	0.91
Breast cancer	0.77*
Stroke	1.39
Pulmonary embolism	1.34

(* The authors suggest that this must be confirmed.)

5. The WHI-CACS trial (2007) reported a reduction in the calcium load in coronary arteries in women mean age 55. The results were clear and striking. This surrogate outcome was considered a valid marker of a reduced risk of CHD since coronary calcium correlates well with the extent of underlying atherosclerosis and the risk of future cardiovascular events.

6. A recent analysis of the timing of HRT was published. “Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years since Menopause” (*Practical Pointers* April 2007 [4-4]) This article considered both CEE –alone and CEE + medroxyprogesterone. Both regimens resulted in a slight *reduction* in CHD events in the first 10 years after menopause. CEE-alone was more protective than CEE + MPA. Both regimens were related to an increased risk of stroke regardless of years since menopause.

NEJM June 21, 2007; 356: 2639-41 Editorial, first author Michael E Mendelshon, Tufts-New England Medical Center, Boston Mass.

Back To Basics

6-4 SOCIAL MEASURES MAY CONTROL PANDEMIC FLU *A Message from a Recent Conference In Barcelona*

Non-pharmacological interventions may be as important as, or even more important than, drugs and vaccines in fighting pandemic flu.

An international conference on health technology assessment heard from James LeDuc, a professor at the University of Texas who until recently helped to lead the US national strategy for responding to pandemic flu. He reported how St Louis did much better than Philadelphia in the 1918 pandemic—long before effective drugs and vaccines were available.

St Louis had its first cases on 5th of October 1918. On October 7, it took a range of measures such as closing schools, theaters, and dance and pool halls, and banning public gatherings, including funerals.

Philadelphia had its first cases on September 17. On September 28, a citywide parade was held. Philadelphia did not act until October 3.

St Louis experienced fewer cases of flu and had a much lower increase in the number of cases.

Comparisons of the spread of flu in other US cities in 1918 supported the case for “social distancing”.

Some scientists have proposed that a pandemic might be prevented by drug treatments on a “massive scale” when it becomes clear that the virus is beginning to spread. The success of such a strategy would depend on first class surveillance, international cooperation, adequate human resources and funding, and possibly a huge transfer of drugs from one country to another.

“Social distancing” will be important to help reduce the numbers of cases and also to slow the spread of the epidemic, buying time for production of a vaccine.

The virus that eventually causes the next pandemic may not be a variant of H5N1, as has been widely expected, but another strain altogether. By the time the pandemic arrives, (and everyone thinks it is inevitable) the virus may be resistant to the drugs now available.

BMJ June 30, 2007; 334: 1341 Commentary by Richard Smith, Chair of the conference on pandemic flu.

“Gonococcus is an incredible bug because it adapts incredibly quickly.”

6-5 GONOCOCCAL INFECTIONS

Update from the CDC Fluoroquinolones no longer recommended

Fluoroquinolones (eg, ciprofloxacin) were recommended for treatment of gonorrhea beginning in 1993. Now prevalence of fluoroquinolone resistance is increasing. Resistance spread from the Pacific region to California, and now is prevalent across the country.

The present recommendations:

1) Uncomplicated gonorrheal infections of the cervix, urethra, and rectum:

Ceftriaxone (Rocephin; Roche) 125 mg single i.m. dose, or

Cefixime (Suprax; Lupin) 400 mg in single oral dose. (Available only in a suspension of 200 mg per 5 mL)

2) Plus treatment for Chlamydia if this infection is not ruled out:

Azithromycin (Zithromax; Pfizer) 1 gram oral single dose, or

Doxycycline 100 mg orally twice a day for 7 days.

JAMA June 13, 2007; 297: 2466-68 quoted from MMWR report from the CDC 2007;56: 336

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“It Is A Perverse Public Health Policy That Makes An Addictive Drug Widely Available In Its Most Harmful Form, Yet Bans Or Fails To Properly Inform Consumers Of Availability Of That Drug In A Much Less Harmful Form”

6-6 SNUS—What should the public health response be?

Global cigarette production continues to increase. In most developed countries, about a fifth of annual deaths are caused by smoking. Many people have a serious smoking-caused illness each year, the most being respiratory diseases.

Snus, a form of smokeless tobacco, has lower levels of toxins than most other smokeless tobaccos. Snus has been estimated to be 90% less harmful than cigarettes. It has become the dominant form of tobacco used by Swedish men, who now have an unusually low smoking rate.

We should carefully consider the potential public health impact of snus.

Two articles concerning snus appear in this issue of Lancet.^{1,2}

1 This study reports the risks of 3 types of cancer in a cohort of 280 000 Swedish male construction workers followed for 20 years:

1) Oral cancer: Relative to never-tobacco-users, snus use did *not* increase risk of oral cancer.

Cigarettes doubled the risk

2) Lung cancer: In this study, snus users had a slightly *lower* risk of lung cancer than never-tobacco-users. Cigarette smokers had 10 times the risk.

3) Pancreatic cancer: A novel finding—snus users had twice the risk of pancreatic cancer as never-

tobacco-users. But, again, risk was higher for cigarettes. Most subjects who developed pancreatic cancer did so before the 1980s. Since then, levels of carcinogens in snus have been reduced.

- 2 This study estimated the likely health impact of snus in Australia. (Snus is currently banned in the European Union, apart from Sweden, and also in Australia.)
 - 1) Snus is likely to produce a net benefit to population health, with the size of the benefit dependent on how many inveterate smokers switch to snus.
 - 2) This challenges the wisdom of banning snus where cigarettes are widely used. It encourages public health professionals to disclose accurate health information on the relative risks of snus compared with cigarettes.

Snus is not harmless. It can cause gingival recession and adverse outcomes in pregnancy. There is conflicting evidence about cardiovascular risks. However, for all the major smoking-related diseases, the risks are lower with snus than with smoking. Importantly, snus poses *no risk* for lung cancer and chronic obstructive pulmonary disease.

Sometimes if a product is found to be “not safe”, this may be grounds for banning the product. Such an absolutist position can ignore the complex realities of many of the most important health risks we face. Exposure to any level of risk from tobacco products such as snus can seem an unnecessary risk. “We consider the appropriate response is to inform consumers and encourage alternatives while respecting individual choices.” “Public policy should aim to strongly discourage highly dangerous behaviors, and provide appropriate information and warnings about lower-risk behaviors.” “It is a perverse public health policy that makes an addictive drug widely available in its most harmful form, yet bans or fails to properly inform consumers of availability of that drug in a much less harmful form (for both the consumer and those around them).”

“We believe it is preferable that, if people become addicted to cigarettes or decide to try tobacco, they can use a product that is markedly less harmful than cigarettes.” In Sweden, primary use of snus is associated with reduced risk of cigarette smoking. “We should not delay in allowing snus to compete with cigarettes.” “We should be prepared to accurately inform smokers about the relative risks of cigarettes, snus, and approved smoking-cessation medications.”

The editorialists are not suggesting that clinicians advise their smoking patients to switch to snus when safe and effective medications are available to treat cigarette dependence. They recommend that clinicians advise their smoking patients to quit smoking with the help of existing approved medications, rather than snus.

Lancet June 16, 2007; 369: 1976-78 Commentary, first author Jonathan Foulds, University of Medicine and Dentistry of New Jersey—School of Public Health, New Brunswick.

1 “Oral Use of Swedish Moist Snuff (snus) and Risk of Cancer of the Mouth, Lung, and Pancreas in Male Construction Workers” Lancet June 16, 2007; 369: 2015-20 First author Juhua Luo, Karolinska Institutet, Stockholm, Sweden

2 “Assessment of Swedish Snus for Tobacco Harm Reduction: An Epidemiological Modeling Study” Lancet June 16, 2007; 369: 2010-14 First author Coral E Gartner, University of Queensland, Australia.

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Communication Into One Manageable Channel

6-7 COMMUNICATION BETWEEN PHYSICIANS AND PATIENTS IN THE ERA OF E-MEDICINE

Clinics are beginning to invite patients to use a *secure* Internet link to communicate with physicians and staff members. The field is evolving swiftly.

Patients have become accustomed to contact physicians' offices through myriad routes: telephone, hospital paging systems, physicians' cell phones, fax machines, and in some cases, physicians' home phones.

Web messaging is an attempt to direct round-the-clock communication into one manageable channel.

One problem was that, since privacy could not be secure, the use of standard e-mail to communicate with patients is illegal—a violation of the laws protecting patients privacy.

In addition to secure Web messaging, an e-medicine model could comprise 4 major types of services:

1) online appointment scheduling, 2) electronic prescription refills, 3) general messaging capabilities, and 4) "Web visits" with physicians. General messages permit patients to ask simple questions, obviating many telephone calls. "Web visits" are structured consultations focused on non-urgent chief complaints involving menus of questions tailored to the problem, brief answers by the patient, and a response from the physician within a certain period.

"With the growing acceptance of e-medicine by third party payers, a quiet revolution has begun." Some insurance companies now reimburse physicians for Web visits.

Early studies indicate that e-medicine methods improve productivity of providers, reduce the number of office visits, and save money.

Patients who are comfortable with the Internet delight in e-medicine's prospect of convenient access to doctors. Most patients became frustrated long ago by telephone calling trees, voice mail, and interminable waits on hold.

A survey in 2006 indicated a strong preference among a majority of respondents for access to a variety of e-medicine technologies in communicating with their doctors and hospitals. But many patients do not expect to pay for this expanded service. Requests for prescription refills and queries about test results are viewed as extension of visits, and are generally free. The expenses that patients incur in attending clinic visits—time away from work, cost of travel, parking fees, and the co-payment—make Web visits for non-urgent problems an attractive option for some. Nevertheless, third-party payers will have to begin underwriting the cost of Web visits before patients avail themselves of this option.

Staff members, who are usually the first point of contact for patients, tend to embrace e-medicine whole heartedly. The use of e-mail for routine tasks, such as prescription refills, and appointment scheduling, reduces clinics' call volume. This gives staff members more time to serve patients who have urgent needs.

E-medicine may also enable hospitals to improve transitions of care of patients. Flawed transitions of care can lead to mistakes that have serious consequences.

A growing number of companies seek to capitalize on secure communication products.

The federal government has set out a National Information Technology plan with a goal of establishing electronic health records systems for most Americans by 2014.

What do doctors think? Many appreciate the asynchronous nature of Web messaging. Patients contact doctors at their convenience. Physicians respond when they have a moment. Most physicians find it much easier to respond to queries in this form than to return phone calls.

The emerging model will improve the practice of medicine, but will also bring new challenges. E-medicine will demand from physicians astute judgment about which patients need to be evaluated in person, and sound intuition about when patients' emotional needs are better served face-to-face. In the end, e-medicine will remain a human enterprise, filled with the potential for misinterpretation and insensitivity, but also for facilitation, comfort, and kindness. "It is our task to ensure that e-medicine—now inevitable in some form—improves the ways in which we deliver, receive, and pay for health care."

"The 'laying on of hands' will increasingly include the 'pressing of keys'.

NEJM June 14, 2007; 356: 2451-54 "Perspective", Commentary by John H Stone, deputy editor at UptoDate, Waltham, Mass

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"Our Findings Remain To Be Confirmed."

6-8 EFFICACY OF FOLIC ACID SUPPLEMENTATION IN STROKE PREVENTION: A meta-analysis

Initial epidemiological evidence supported the hypothesis linking elevated homocysteine levels with increased risk of coronary artery disease, stroke, and deep vein thrombosis. And that treatment with folic acid reduced risk.

Randomized trials have reported inconsistent results, and have not supported the hypothesis that lowering homocysteine reduces risks. Most of these trials have been conducted in patients with established cardiovascular disease. It is possible that folic acid supplementation could have a greater protective effect in primary rather than in secondary prevention. And that different cardiovascular endpoints could respond differently to folic acid. A population-based study conducted following folic acid fortification of foods reported that decline in stroke mortality occurred after fortification was instituted.

This meta-analysis focused on stroke as the disease endpoint in relation to folic acid supplementation.

Conclusion: Supplementation with folic acid as primary prevention was related to reduction in risk of stroke.

STUDY

1. Collected data from 8 randomized trials (over 16 500 individuals, most over age 60) of folic acid (with or without B6 and B12) supplementation vs placebo. All reported stroke as one of the endpoints. All trials included individuals with pre-existing cardiovascular or renal conditions.
2. Dose of folic acid in the intervention groups ranged from 0.5 mg/day to 15 mg/day. Duration of trials from 24 to 72 months.
3. Baseline homocysteine levels varied considerably.

RESULTS

1. Homocysteine levels were reduced in the treatment groups in all trials, but to a varying degree, from 2 umol/L

to 15 umol/L

2. Pooling results of all trials indicated a statistically significant reduced risk of stroke in the folic acid treatment groups. (Relative risk [RR] = 0.82; folic acid vs placebo).
3. Longer-duration trials were associated with greater benefit in reducing stroke. Less than 36 months RR = 1.0; longer than 36 months RR = 0.71.
4. In the one study of subjects with a history of stroke the RR = 1.04 vs a RR of 0.75 in 7 studies of subjects without a history of stroke (but with other vascular diseases).
5. Reduction in risk was greater in trials reporting a greater reduction in homocysteine levels.

DISCUSSION

1. “Our meta-analysis provides coherent evidence that folic acid supplementation can significantly reduce the risk of stroke in primary prevention.”¹
2. “The inverse relation between the duration of folic acid supplementation and the risk of stroke suggests that the effect of folic acid supplementation on the risk of stroke is probable causal.”
3. “Additional evidence for a causal relation is provided by our observation that, in countries where grain is fortified with folic acid, further supplementation of the diet with folic acid had little effect on the risk of stroke; by contrast, folic acid supplementation significantly reduced risk of stroke in countries where grain was not fortified.”
4. “Our meta-analysis showed that a decrease of less than 20% in the concentration of homocysteine did not significantly affect the RR of stroke, whereas a significant reduction in the RR of stroke occurred with a decrease in homocysteine concentrations of 20% and more.” “This dose-response relation provides further evidence that homocysteine reduction could serve as a surrogate biomarker for reduction in risk of stroke.”
5. There is continued controversy with regard to whether folic acid can lead to improved outcomes for other cardiovascular endpoints. Several randomized trials of folic acid supplementation have in general yielded negative results. However, different endpoints (eg stroke vs other cardiovascular endpoints) could respond differently.
6. “Our findings remain to be confirmed.”

CONCLUSION

“Our findings indicate that folic acid supplementation can effectively reduce the risk of stroke in primary prevention.”

Lancet June 2, 2007; 369: 1876-82 Original investigation, first author Xiaobin Wang, Northwestern Feinberg School of Medicine, Chicago, IL. (Prof. Wang is also connected to Anhui Medical University, Hefei, China)

1 I do not believe that this meta-analysis should be termed a study of “primary prevention”. No subjects were free of atherosclerotic disease at baseline. A true “primary prevention” trial should be based on subjects without atherosclerotic disease at baseline.

An editorial in this issue of Lancet by Cynthia M Carlsson, University of Wisconsin School of Medicine, Madison, comments and expands:

The homocysteine-folic acid connection for reduction of cardiovascular disease is controversial. While increased concentrations of total plasma homocysteine have been associated with vascular abnormalities and CVD events in observational studies, several clinical trials and a meta-analysis reported that folic acid does not improve CVD outcomes.

Despite these negative findings, important questions remain:

The effect of lowering homocysteine longer term.

Use of folic acid in primary preventions of CVD (again long-term).

The effect of supplementation on specific endpoints (eg stroke vs CHD).

The editorialist states that this meta-analysis cannot provide definitive evidence that homocysteine lowering has a role in primary prevention of stroke.

Moderate Effectiveness In Clinical Practice

6-9 CARDIAC RESYNCHRONIZATION THERAPY FOR PATIENTS WITH LEFT VENTRICULAR SYSTOLIC DYSFUNCTION A Systematic Review

Despite many advances, for many patients with heart failure (**HF**), morbidity and mortality remains high, and quality-of-life is poor. “Thus, there is increasing enthusiasm for the therapeutic potential of atrial-synchronized biventricular pacemakers (cardiac resynchronization therapy; **CRT**) in patients with heart failure and left ventricular (**LV**) systolic dysfunction.”

CRT is designed to eliminate the delay in activation of the left ventricular free wall found in many patients with LV systolic dysfunction (inefficient contraction of the ventricle manifested by a prolonged QRS), and thereby to improve mechanical synchrony, which in turn increases left ventricular filling time, reduces mitral regurgitation, and reduces septal dyskinesis.¹

This review summarizes the current evidence regarding the efficacy (outcomes in randomized trials) and effectiveness (outcomes in clinical settings), and safety of CRT in patients with LV systolic dysfunction.

Conclusion: When combined with optimal pharmacotherapy, CRT reduces morbidity and mortality in patients with LV systolic dysfunction, prolonged QRS duration, and class 3 or 4 symptoms

STUDY

1. Literature search found 14 randomized controlled efficacy trials (4420 patients); 106 observational (effectiveness) reviews (9200 patients); and 89 safety reviews (9600 patients).
2. Randomized, controlled trials (**RCTs**):
 - A. All patients in the randomized controlled trials had LV systolic dysfunction (left ventricular ejection fraction 21% to 30%); prolonged QRS duration (range 155 to 209 milliseconds), and HF symptoms.
 - B. The RCTs attempted to ensure participants were treated with optimal pharmacotherapy (ACE inhibitors

or angiotensin II blockers, beta-blockers, and spironolactone in eligible patients) at baseline. All comparisons were CRT + pharmacotherapy vs pharmacotherapy alone. Mean age 65; 72% male. About half received CRT alone; half CRT + implantable cardioverter-defibrillator.

C. All but 2 trials reported industry funding.

2. Efficacy of CRT in RCTs:

A. In the RCTs, 59% of CRT recipients improved at least one NYHA class vs 37% of controls.

B. Compared with controls, left ventricular ejection fraction increased by 3%; 6-minute walk test distance increased by 24 meters; and quality-of-life increased by 8 points on a living with heart failure questionnaire.

C. Hospitalizations for HF were less frequent in the CRT subjects (19% vs 27%).

D. All cause mortality 13% vs 15%. The survival benefit was largely due to reductions in progressive HF deaths.

3. Observational (effectiveness) studies:

A. All patients had LV systolic dysfunction

B. All had prolonged QRS (range 140-206 milliseconds)

C. All had HF symptoms at baseline.

4. Effectiveness of CRT (observational studies in clinical practice):

Improvements in function and survival over time was similar to those reported by RCTs.

5. Safety:

Implantation success = 93%; peri-implantation mechanical complications 4%; peri-implantation deaths 0.3%;

5% malfunctioned within 6 months; 2% hospitalized for infections in the implant site; lead problems in 7%.

6. About 1% to 3% of all patients discharged alive after their initial hospitalization for HF meet CRT trial criteria:

LVEF < 35%

QRS > 120 milliseconds

Sinus rhythm

NYHA class 3 or 4 despite optimal medical therapy

7. An important question is whether the efficacy of CRT in randomized trials translates into effectiveness in clinical practice. It is possible that benefits of CRT may be overestimated and risks underestimated. Relying on eligibility criteria to define those patients most likely to benefit is not perfect. More than one third of recipients do not exhibit any functional or echocardiographic improvements after activation of their CRT. In particular, QRS duration has been used to select patients. Thus far, it is uncertain whether, and to what extent, the use of newer techniques to detect electromechanical dyssynchrony will impact the effectiveness and safety of these devices.

CONCLUSION

CRT is efficacious in clinical practice, and is cost-effective therapy for patients with class 3 or 4 HF (despite optimal medical management), and a LVEF less than 35%, sinus rhythm, ventricular dyssynchrony (currently identified by a prolonged QRS duration).

CRT improves ventricular function and remodeling, improves symptoms and exercise capacity while reducing frequency of HF hospitalizations, and death. The magnitude of these benefits is similar to those reported for ACE inhibitors or beta blockers, and are additive to the benefit of such medical therapy.

Risks (noted above) should be factored into clinical decisions about whether to refer a patient. Implantation can be technically challenging (especially placement of the left lead). Even when lead placement is thought to be successful, CRT does not always restore mechanical synchrony.

JAMA June 13. 2007; 297: 2503-14 Systematic review, first author Finlay A McAlister, University of Alberta, Canada.

1 With bundle-branch-block and lengthened QRS, the left ventricle contraction is inefficient. The purpose of the Purkinje network LOOK UP is to depolarize all portions of the ventricle simultaneously to produce a coordinated, efficient contraction. The pacemaker is an attempt (albeit not very efficient) to replace the Purkinje system.

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Can Set A Positive Tone For The Encounter

6-10 AN EVIDENCE-BASED PERSPECTIVE ON GREETINGS IN MEDICAL ENCOUNTERS

The first few moments of a medical encounter are critical for establishing rapport, making the patients feel comfortable, and setting the tone of the interview. However, there is little evidence regarding patient perspectives of what constitutes an appropriate greeting.

The purpose of this study was to provide some guidance by defining patient-expectations for physician behavior during the greeting stage of the initial medical visit.

Conclusion: Physicians should be encouraged to shake hands, and initially use patient’s first and last names, and introduce themselves with their own first and last names.

STUDY

1. Conducted a cross-sectional random telephone survey of adults (ie, patients) in the US. (415 persons responded.) Asked closed-ended questions about their preferences for shaking hands, use of the patient’s names, and use of physician’s names, especially at the first meeting.
2. Conducted a separate video tape of actual initial meetings.

RESULTS

1. Behavior	Telephone survey (n = 415) (Patients’ preference)	Video tape (n = 123) (Actual performance)
Dr. to shake hands		
Yes	78%	83%
No	8	17
Dr. use of patient’s names		
First only (eg, “Jane”)	50	14

Last only (eg, “Ms Smith”)	17	32
Both	24	3
Not mentioned by physician		50
Dr. use of their own names		
First (eg, “Bob”)	7	0
Last (eg, Dr. Franklin”)	32	30
Both	56	58
Not mentioned by physician		11

2. No statistically significant differences regarding use of patient names across patient age, sex, race/ethnicity, or educational level.
4. Most patients wanted physicians to use their (physicians’) first and last names during the initial visit.
5. More females and African Americans preferred physicians to use their (patients’) first and last names.
6. In response to open-ended questions the most common responses of respondents were: smile; be friendly; be personable; polite; respectful; attentive; calm; make patient feel like a priority; and make eye contact.

DISCUSSION

1. “While greetings may seem a rather mundane aspect of physician-patient communication, attention to this task can set a positive tone for the encounter, and increase the chances of developing a therapeutic clinical relationship.”
2. The finding that older patients were somewhat *less* likely to express a preference for shaking hands reinforces the importance of being sensitive to non-verbal cues that might indicate whether patients are open to this behavior.¹
3. “Of course, physicians should maintain safety and hygiene by washing their hands.”
4. The investigators’ suggestions:
 - Physicians should initially use patients’ first and last names.
 - (African-Americans may prefer a more formal address in subsequent encounters.)
 - Physicians should introduce themselves using their first and last names.
 - (Adopting this strategy of using parallel identity terms communicates respect and reciprocity.)
5. The investigators recommend asking about patient’s preferred address at the point of using their name a second time.
6. The investigators did not ask whether patients want physicians to explain their role (eg, nurse, resident or specialist). But this is an essential component of the introduction, particularly when providers may have different levels of training and different responsibilities.
7. On return visits, the investigators suggest that previous meetings be acknowledged during the greeting “Hello, Mrs. Smith, good to see you again. I am Janet Jones, a resident working with Dr. Franklin.” Greetings in return visits can convey a great deal about how much a physician remembers or cares about a patient.
8. Over time, the type and tenor of greetings will vary depending on the context of care and depth of the physician-patient relationship.

9. Because greetings are one way to ensure proper identification, they might well be considered a fundamental component of patient safety.

Archives Int Med June 11, 2007; 167: 1172-76 Original investigation, first author Gregory Mahoul, Northwestern University School Feinberg School of Medicine, Chicago. IL

1 This is contrary to my experience. The elderly I know are quite willing to shake hands

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A Remarkable Pioneering Technique Which May Provide Comfort To Many Women

6-11 AUTOLOGOUS MYOBLASTS AND FIBROBLASTS VERSUS COLLAGEN FOR TREATMENT OF STRESS URINARY INCONTINENCE IN WOMEN

The most common causes of urinary incontinence are 1) urge incontinence (excessive activity of detrusors), and 2) stress incompetence (intrinsic sphincter insufficiency) of the urethral sphincter complex—the urethra and the striated rhabdosphincter (under voluntary control). Stress incontinence is more common than urge incontinence.

Factors that affect closure of the urethra include urethral smooth and striated muscle tone and the supportive properties of the urethral mucosa and submucosa (especially the vascular submucosal layer). Poor muscle function, due to atrophy and reduced vascularization, might contribute to stress incontinence, especially in elderly women with low estrogen levels. The role of the striated urinary sphincter (the rhabdosphincter) is pivotal. The rhabdosphincter is a muscular coat that surrounds the urethra at its ventral and lateral aspects. It is integral to the urethral closure mechanism. The resting tone and contractility of the rhabdosphincter are reduced in incontinent patients. The urethra does not close completely. Damage to this muscle can result from maternal injury during childbirth, or from surgical injury. Spontaneous apoptosis also contributes to an age-dependent loss of the striated muscle cells of the rhabdosphincter.

Conventional surgical procedures are successful in treating incontinence in 80% of patients one year after surgery. But continence rate declines with age. Injection of collagen into the periurethral tissue to compress the urethra and thus occlude the urethral lumen is a standard technique for incontinence, but overall success rates are poor. Standard treatments do not address the pathophysiological causes of incontinence.

Myoblasts taken from skeletal muscle have the same physiological properties as those from the rhabdosphincter. Myoblasts have adult tissue stem cell potential. They can proliferate and form new muscle tissue. Injected autologous myoblasts and fibroblasts have been used to aid the regeneration of skeletal muscle tissue. No serious adverse effects have been reported after implantation of such cells.

A new injection device which uses transurethral ultrasonography as a guide has been designed to allow more precise injection into the urethra and rhabdosphincter.

This study investigated whether transurethral ultrasound-guided injection of autologous myoblasts and fibroblasts could promote regeneration of the rhabdosphincter, combat atrophy of the urethral submucosa, and relieve stress incontinence.

Conclusion: In a small series, this technique was successful in a high percentage of women.

STUDY

1. Randomized 63 women (age 36 to 84) with stress incontinence to 1) transurethral ultrasonographically guided injections of autologous myoblasts and fibroblasts, or 2) conventional endoscopic injections of collagen. No subject had urge incontinence. All had done pelvic-floor exercises before randomization without improvement.
2. Muscle tissue was obtained by biopsy of the upper arm. Muscle tissue was separated from connective tissue. Both were processed and plated on standard tissue-culture flasks and incubated. At 6 to 8 weeks of culture, fibroblasts and myoblasts were harvested separately. (See page 2181 for details.)
3. For the 42 patients randomized to treatment of autologous cells, an ultrasonography transducer was inserted into the urethra to visualize the urethral wall and rhabdosphincter. Each subject's autologous myoblasts were injected into her rhabdosphincter at multiple sites; fibroblasts were injected circumferentially into the submucosa. For those assigned to collagen injections, standard techniques were used.
4. Patients continued regular training of the rhabdosphincter for 12 weeks and transvaginal electrical stimulation for 4 weeks after the operations.
5. Primary outcomes = an incontinence score, contractility of the rhabdosphincter, and the thickness of both urethra and rhabdosphincters.

RESULTS

1. At 2 months 38 of 42 women injected with autologous cells were completely continent vs 2 of 21 given conventional treatment with collagen.
2. The median continence score decreased from a baseline 6.0 (complete incontinence) to 0 (complete continence) for patients treated with autologous cells. The median score for patients receiving collagen remained at 6.0.
3. Ultrasound showed the mean thickness of the rhabdosphincter increased from 2.3 mm to 3.4 mm in those receiving autologous tissue.
4. Contractility of the rhabdosphincter increased from baseline in the autologous group. (*See illustrations page 2182-84-85.*)
5. Thickness of the urethra increased in both groups after treatment with no significant difference between treatment groups.
6. Coaptation of urethral submucosa was noticeably improved after treatment with autologous cells.
7. Quality-of-life improved in the autologous-cell group.
8. No adverse treatment effects were reported. No postoperative obstruction was recorded in either group.

DISCUSSION

1. Ultrasonographic, electromyographic, and clinical results in the group treated with autologous cells suggest that the injection of myoblasts and fibroblasts led to regeneration of the rhabdosphincter and submucosa.
2. In the autologous-cell group, periurethral electromyography revealed increased activity of the rhabdosphincter resulting in increased resting tone and voluntary contractile force. "This finding suggests that additional muscle tissue was formed in the rhabdosphincter."

3. Combined regeneration of both the rhabdosphincter and the urethra seem to be needed for improved closure of the urethral lumen.

CONCLUSION

“Long-term postoperative results and data from large numbers of patients are needed to assess whether injection of autologous cells could become standard treatment for urinary incontinence.”

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