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THE RENIN-ANGIOTENSIN SYSTEM AND CARDIOVASCULAR DISEASE

ANGIOTENSIN-II BLOCKER PROVIDES ADDITIONAL BENEFITS WHEN ADDED TO OTHER DRUGS TREATING HYPERTENSION, HEART FAILURE, AND CORONARY HEART DISEASE

ACUPUNCTURE: A Clinical Conference

POST MENOPAUSAL HORMONE THERAPY: Relation to CHD and Stroke.

MORPHINE KILLS THE PAIN, NOT THE PATIENT

BEING OVERWEIGHT MAY NOT BE SO BAD FOR THE ELDERLY

BREAST CANCER SCREENING FOR WOMEN IN THEIR 40s

COMBINATION SUMATRIPTAN-NAPROXIN FOR MIGRAINE

PHYSICIANS' CONSIDERATION OF PATIENT'S' COSTS

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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 5 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
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HIGHLIGHTS AND *EDITORIAL COMMENTS* APRIL 2007

"Best Proven Interventions to Reduce Target Organ Damage in Hypertension, Atherosclerosis, and Diabetes."

4-1 RENIN-ANGIOTENSIN SYSTEM AND CARDIOVASCULAR RISK

The renin-angiotensin system (**RAS**) is a major regulatory system for cardiovascular and renal function.

Angiotensin-converting enzyme inhibitors (and by extension, angiotensin-II blockers) have been described as having the broadest effect of any drug in cardiovascular medicine.

This review article begins with a brief description of the biology or the renin-angiotensin system.

It continues with consideration of the relation between RAS and:

1) Left ventricular hypertrophy
2) Atrial fibrillation
3) Stroke
4) Atherosclerosis
5) Type-2 diabetes.

"ARBs and ACE inhibitors are best proven interventions to reduce target organ damage in hypertension, atherosclerosis, and diabetes."

Conclusion: Improvement in the patient's cardiovascular risk by drugs which attenuate activity of the renin-angiotensin system is not related to BP reduction alone. Risk-reduction includes many other non-hemodynamic effects.

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Read the full abstract.

I believe these ACE inhibitors and angiotensin II blockers have become major therapeutic interventions in primary care. Clinicians should become thoroughly familiar with their actions and benefits. And prescribe them more frequently.

There is much to lead primary care clinicians to choose angiotensin-II blockade (over ACE inhibition). ARBs are much better tolerated than ACE inhibitors. They are not associated with the annoying dry cough and angioedema produced by ACE-inhibitors

"Prevented More Cardiovascular Events than Supplementation of Conventional Treatments"

4-2 VALSARTAN IN A JAPANESE POPULATION WITH HYPERTENSION AND OTHER CARDIOVASCULAR DISEASE: The Jikei Heart Study

This study investigated whether addition of the angiotensin-II blocker, valsartan (*Diovan*; Novartis) to conventional cardiovascular treatment is effective in Japanese patients with cardiovascular disease.

The cardiovascular diseases in this study population—heart failure, hypertension, and coronary heart

disease—are all disorders in which activation of the renin-angiotensin-aldosterone system is thought to play a major part.

Randomized, controlled trial entered over 3000 Japanese patients (mean age 65). All were undergoing conventional treatment for hypertension, CHD, HF, or a combination of these disorders.

Randomized to: 1) valsartan [40 to 160 mg daily], or 2) controls.

Controls were given either an increased dose of their existing treatment, or an additional conventional treatment, to achieve BP control aimed at 130/80. (Drugs at baseline, and continued during the trial, included calcium blockers, ACE inhibitors, beta-blockers, alpha–blockers, thiazides, statins, and fibrates. ACE inhibitors were given in about 1/3 of patients, and were continued in both groups.)

Primary outcome = composite of cardiovascular morbidity and mortality. Analysis by intention to treat. Follow-up for 3 years.

Mean BP for both groups at 3 years = 132/77

Effects on all endpoints (rate per 1000 patient-years):

	Valsartan	Control	NNT
Composite endpoint	21 (6.0%)	35 (9.7%)	27
Stroke or TIA	8	11	
Angina pectoris	4	12	
New HF or exacerbation	4	8	
Dissecting aneurysm	0.5	2.3	
All cause mortality	6.5	6.3	

Mortality, myocardial infarction, or progression of renal disease did not differ between groups.

Conclusion: The addition of valsartan to conventional treatment prevented more cardiovascular events than supplementation of conventional treatments. These results cannot be explained by a difference in BP control

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I believe that primary care clinicians should give ACE inhibitors and AT-II blockers (preferably the latter) the benefit of the doubt, and prescribe them more frequently. Their overall benefits (see the preceding abstract) exceed the benefits resulting from other BP-lowering drugs.

"How Acupuncture Works Is Not Readily Understood"

4-3 ACUPUNCTURE: A Clinical Conference

The limited ability of many commonly used interventions to reduce pain and improve function, combined with significant adverse effects of some drugs. has led many patients to try therapies outside the mainstream of medicine. A National Health Survey reported that 41% of respondents with arthritis had used some form of complementary-alternative medicine.

"The perception of acupuncture as a legitimate medical intervention expanded when the National Institutes of Health and the FDA held consensus development and technological assessment conferences (1998) that

resulted in recommendations on the potential use of acupuncture, in particular for pain-related conditions, as well as post-operative and chemotherapy-induced nausea and vomiting, and when the he FDA reclassified acupuncture needles from investigational devices to medical devices."

Surveys of rheumatologists and pain specialists reported that 56% to 84% considered acupuncture a legitimate medical practice.

From the Western medical viewpoint, how acupuncture works is not readily understood. "High-quality evidence evaluating CAM has been scarce."

The discussant focuses on the role of acupuncture relative to other treatments for the pain of osteoarthritis.

Randomized trials (acupuncture vs sham acupuncture) have reported contradictory efficacies. The benefits of some of the other knee osteoarthritis treatments (eg, intra-articular corticosteroids relative to placebo) are larger than the effects of acupuncture (relative to sham acupuncture). "The definition of appropriate sham acupuncture is still not resolved."

There are a wide variety of schools of acupuncture, ranging from traditional Chinese methods to Western styles. Japanese and Chinese acupuncture are very different. As a consequence, there are many distinct styles of practice. Points of acupuncture vary. Points chosen for treatment vary from treatment to treatment. Variations include depth of needle penetration, the number of needles used, diameter and length of the needles, and the length of time needles are left in place. Different types of needle stimulation are used—manual, heat, electrical.

Most clinicians use multidisciplinary approaches to the management of osteoarthritis, recognizing that most available treatments have small effects. Different treatments used concurrently may provide incremental improvements. Adding acupuncture may increase costs Some patients respond; some do not.

Cultural factors, which include expectations and beliefs, are extremely important influences on the outcomes of many treatments, acupuncture included.

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I enjoyed this article. I abstracted it in detail to enhance my understanding. I came away with the following thoughts:

There is no such thing as "acupuncture". There are acupuncture(s). There is no standard on which to base determination of efficacy.

There is no established biological basis for belief that acupuncture is more than a placebo effect.

There is no good evidence for other than short-term effects (6 to 12 months). Long term benefits are not reported.

I would not deny the power of the placebo. Indeed, all primary care clinicians rely on it to some degree every day. The power of the placebo rests on patient- and physician-beliefs and enthusiasm.

Would I prescribe or advise acupuncture? No. But I would not deter any patient from trying it if the patient requests it and believes it may provide some relief. (Likely based on enthusiastic reports of friends and relatives.)

Hormones Remain A Reasonable Option For The Short-Term Treatment Of Menopausal Symptoms.

4-4 POSTMENOPAUSAL HORMONE THERAPY AND RISK OF CARDIOVASCULAR DISEASE BY AGE AND YEARS SINCE MENOPAUSE

This study (a secondary analysis) explored whether the effects of hormone therapy on risk of cardiovascular disease (**CVD**) vary by age or years since menopause.

The WHI trials enrolled over 27 000 predominantly healthy postmenopausal women aged 50 to 79.

Over 10 000 had undergone hysterectomy and received conjugated equine estrogen-alone (0.625 CEE-alone) vs placebo.

Over 16 000 received CEE + medroxyprogesterone (CEE 0.625 mg + MPA 2.5 mg) vs placebo.

CEE-alone

No indication that it is a risk factor for CHD up to 20 years after menopause. Risk increases at age 70

Associated with increased risk of stroke at all ages.

CEE + MPA:

No indication that it is a risk factor CHD up to 10 years after menopause. Risk increases after 10 years.

Associated with increased risk of stroke at all ages.

Conclusion: Women who initiated HRT closer to menopause tended to have reduced risk of CHD. Risk increased in women more distant from menopause. The risk of stroke was elevated regardless of years since menopause.

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The article did not list baseline risk factors. I would expect that women who developed HRT-associated cardiovascular events would be at higher risk if they had more risk factors at onset of menopause. (Eg, smoking, hypertension, dyslipidemia). Indeed, women without risk factors who take HRT would probably be at lower risk for events than women who do not take HRT, but have a number of risk factors.

I am sure the authors would recommend use of HRT at the lowest dose and for the shortest period.

Progesterone (not estrogen) seems to increase risks of CHD and breast cancer. Both are related to increased risk of stroke.

"Under-Prescribing Of Opioids Remains A Major Barrier To Effective Pain Control"

4-5 MORPHINE KILLS THE PAIN, NOT THE PATIENT

Public and professional anxieties about the effects of morphine continue to hinder adequate access to analgesia. The best known fact about morphine among the public is that it can be addictive. (In fact, the risk of iatrogenic addiction is under 0.1%.) For physicians, the second best known fact is that morphine can precipitate respiratory depression.

A recent study from the US National Hospice Outcomes Project compared opioid use and survival at the end of life. Hospice inpatients (n = 725) with end-stage cancer, lung disease, or heart disease were followed up

to death. The length of stay was *positively* correlated with the maximum daily opioid dose received, even when that dose exceeded 15 times the average for patients in the UK. Neither absolute dose nor change in dose was linked to shortened survival.

Patients who are given the incremental dose-titration practiced in palliative care centers are not at risk of respiratory depression.

Under-prescribing of opioids remains a major barrier to effective pain control. "Physicians should be encouraged to use opioids effectively to relieve suffering at the end of life."

"It Would Seem That Becoming Slightly Overweight May Not Be So Bad."

4-6 THE EFFECT OF OBESITY ON DISABILITY VS MORTALITY IN OLDER AMERICANS

This study (Established Populations for Epidemiological Studies of the Elderly) examined the association between BMI and subsequent mortality and incident disability during 7 years, and estimated the effect of BMI on life expectancy and disability-free life expectancy in initially non-disabled persons.

Entered over 12 500 persons age 65 and older (mean = 72) between 1982 and 1993. None were disabled. None had limitations in activities of daily living (**ADL**). Grouped BMI according to NIH obesity standards: < 18.5 underweight; 18-5-24.9 normal weight; 25 to 29.9 overweight; 30 to 34.9 obesity.

Results:

A. Relation between BMIs and <u>mortality</u>: BMIs associated with the minimum hazard of mortality were between 25.1 and 29.9 (overweight). There was a difference between men and women: For men, the total life expectancy was greatest with BMIs between 25 and 29.9. For women it was between 30 and 34.9 (obese).

B. Relation between BMIs and <u>disability</u>: The lowest point-hazard ratio for disability associated with ADL was a BMI of 24. Hazard ratio for disability rose to ~ 1.2 as BMI rose to 27. Hazard ratio for disability rose to ~ 1.2 as BMI fell to 22-23

<u>C. Disability-free life expectancy:</u>

Disability-free life expectancy was greatest among both men and women with a BMI of 25 to 29.9 (overweight). The estimated total life expectancy that will be disability-free fell sharply for subjects with BMI 30 and higher (obese).

Loss of independence is one of the most feared outcomes experienced by older individuals, and is a major contributor to poor quality of life.

The association between elevated BMIs and subsequent disability provides evidence that obesity (BMIs > 30) in older populations is associated with substantial increase in risk of poor health outcomes.

The association between elevated BMI and mortality may be attenuated by selective survival. Elevated BMI is clearly associated with increased mortality at younger ages. It is possible that persons susceptible to increased early mortality associated with elevated BMI die at younger ages, weakening the observed relationship at older

ages. Only about half of the study cohort survived to age 65. Because of the effect of obesity on mortality tends to decline with age, those available to participate in a study of older persons constitute "healthy survivors".

"At the individual level, considering the trade-off between total and disability-free life expectancy, it would seem that becoming slightly overweight may not be so bad."

Conclusion: "Assessment of the effect of obesity on the health of older Americans should account for mortality and incidence of disability."

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If you avoid the risks of being overweight at younger age, and you make it to age 65-70 it may be better to be a little overweight. This may give some of us elders comfort as we age and our daily energy expenditures decline while our food-intake habits remain fixed.

"No Simple Recommendation Applies To All Women In Their 40s"

4-7 BREAST CANCER SCREENING FOR WOMEN IN THEIR 40s: Moving from Controversy about Data to Helping Individual Women

Women in the USA now generally expect that screening should begin at age 40.

For every 10 000 women screened regularly starting at age 40, 6 might benefit through decreased risk of death due to BC. This modest benefit requires multiple screening examinations and follow-up for all 10 000 for more than a decade. Thus, 9994 women receive no mortality benefit because most women will not develop BC, and some will have cancer detected too late for a cure.

What are the potential harms of screening? False positive results are more common in younger women. Among those starting screening at age 40, about half might receive at least one false positive result over a decade of annual screening. Further diagnostic procedures follow, with about 2000 women eventually undergoing a biopsy. Anxiety is increased. Costs are considerable.

"In the field of breast cancer screening, the actual practice of evidence-based medicine becomes deeply entangled with social, political, and economic forces."

Failure or delay in BC diagnosis has been the most common issue in medical malpractice claims against physicians.

"In the face of continuing controversy about evidence, our priority now should be to help women make informed decisions." "No simple recommendation applies to all women in their 40s. We must learn to become comfortable with using the art of medicine to translate the existing science. We must listen carefully to our patient and communicate honestly the benefits and limitations of our imperfect tests."

The Two-Drug Tablet Provided More Favorable Clinical Benefits

4-8 SUMATRIPTAN-NAPROXIN FOR ACUTE TREATMENT OF MIGRAINE

"None of the currently available monotherapeutic agents provides broad coverage of the multiple pathogenic processes in migraine, which is thought to involve multiple neural pathways that appear to be

sequentially activated and sensitized as a migraine attack develops." Multi-mechanism-targeted therapy may confer advantages over monotherapy.

This study compared efficacy and safety of a two-drug, fixed-dose tablet containing a triptan and naproxen vs each as monotherapy, and vs placebo.

Compared with sumatriptan-alone (S), naproxen-alone (N) , and placebo, a pill containing both (S + N):

Provided better relief of headache at 2 hours (NNT = 3; S + N vs placebo)

Provided better sustained relief 2 to 24 hours (NNT = 6; S + N vs placebo)

Reduced incidence of recurrence of headache within 24 hours (NNT = 3; S + N vs placebo)

Reduced use of rescue medication.

Adverse events: dizziness, somnolence, paresthesias, nausea, dry mouth—all from 2% to 5%

No statistically significant differences in overall adverse events between S + N, N-alone, and S-alone

Development of the tablet was motivated by the rationale that concurrent use of two agents with complementary anti-migraine mechanisms might confer additive benefit relative to either alone.

Conclusion: S +N as a single tablet for acute migraine resulted in more favorable clinical benefit than either monotherapy with S or monotherapy with N.

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I was puzzled. The article reported 2 replicate randomized, double-blind studies, Results were similar. Dr. Brandes (personal communication) reported that, for approval of a drug, the FDA requires two trials supplying data and meeting primary end-points. The trials are usually reported separately. The JAMA accepted the results of both trials and permitted publication in one article.

Study supported by GlaxoSmithKline. Obviously the article was slanted to promote the 2 drugs combined in one tablet. I wonder if results would be similar if 2 separate tablets were co-administered. And if costs would be lower.

Physicians Do Not Often Consider Patients' Costs

4-9 PHYSICIAN CONSIDERATION OF PATIENTS' OUT-OF-POCKET COSTS IN MAKING COMMON CLINICAL DECISIONS

Patients face growing cost pressures. Physicians do not often consider issues about costs.

This study analyzed data on how frequently physicians considered their patients' O-O-P costs. Does consideration of O-O-P costs affect clinical decision making?

Asked: How often do you consider an insured patient's O-O-P costs when:

1) Prescribing a generic over a brand-name drug?

2) Deciding the types of tests to recommend ?

3) Choosing between inpatient and outpatient care settings?

78% of physicians reported regularly (always or usually) taking patients' O-O-P costs into account when prescribing generic over brand-name drugs; 51% reported considering the costs in choosing out-patient vs in-patient care settings; 40% did so in selecting diagnostic tests.

Physicians treating patients of lower socio-economic status tended to be more likely to consider costs, as were physicians who had more patients receiving Medicaid.

Conclusion: Physicians do not routinely consider patient's costs.

This is a clinically valid and important consideration.

O-O-P costs are only half of the economic burden. Costs to the government and insurance companies are the other half. Patients eventually pay for both. There is only so much money available for health care. When lower cost services are applied, more funds will be available for additional care.

Primary care clinicians should more often access costs, especially drug costs. Pharmacists in the community may help a great deal in determining costs. Costs are also readily available on the drug store web pages.

Considerable savings can be achieved by use of a pill cutter. Many drugs have a high therapeutic index (eg, statin drugs; antihypertension drugs). A higher dose pill may be cut in half or in quarters for the daily dose. It often makes little difference clinically if the cut-dose varies somewhat from one day to the next.

Many scored pills are available. Patients can easily manage their daily dose by breaking the pill in half. Drug stores do not charge double for a pill which is twice as strong. Indeed, some pills at twice the dose cost very little more.

Free clinics frequently dispense generic drugs only. Anecdotally, patients seem to fare just as well.

ABSTRACTS APRIL 2007

"Best Proven Interventions to Reduce Target Organ Damage in Hypertension, Atherosclerosis, and Diabetes."

4-1 RENIN-ANGIOTENSIN SYSTEM AND CARDIOVASCULAR RISK

The renin-angiotensin system (**RAS**) is a major regulatory system for cardiovascular and renal function.

Angiotensin-converting enzyme inhibitors (and by extension, angiotensin-II blockers) have been described as having the broadest effect of any drug in cardiovascular medicine.

BIOLOGY OF THE RAS:

Our understanding is still not complete. It has grown increasingly complex. The enzyme renin (produced by the kidney) converts angiotensinogen (produced by the liver) into angiotensin-I. Angiotensin converting enzyme (**ACE**) converts angiotensin-I to the active angiotensin-II. Angiotensin II binds to receptors on receptor-cells.

Generation of angiotensin-I and angiotensin-II is not restricted to the systemic circulation. Non-angiotensin converting enzymes might account for a part of the conversion of angiotensin-I to angiotensin-II. Production takes place in vascular and other tissues. An enzyme in the human heart and vascular tissue (chymase), which might account for part of the conversion, has been identified. (Bypassing the effect of ACE.)

The effects of all angiotensin peptides are mediated through specific cell surface receptors. Angiotensin-II type-1 receptor is the classical receptor, which leads to vasoconstriction, stimulation of aldosterone release, sympathetic nerve activity, and inflammation. (*Actually, there are 2 angiotensin-II receptors. Activation of the type-2 receptor leads to somewhat opposing effects. I omitted this information to avoid confusion. See the journal text. RTJ)*

Several classes of drugs inhibit the renin-angiotensin system:

Beta-blockers suppress angiotensin-II formation by inhibiting renin release from the kidney.

ACE inhibitors reduce the formation of angiotensin-II from angiotensin-I by inhibiting ACE.

ACE inhibitors do not affect angiotensin-II generation by non-ACE pathways.

Angiotensin receptor blockers (**ARBs**) antagonize the binding of angiotensin-II to receptors on the cell surface. Blocking the cell receptor by angiotensin-II blockers (ARBs) results in the classical effects noted above

Renin inhibitors are under investigation in phase III trials. They lower BP, and offer the potential to inhibit the entire cascade of the system.

ACE inhibitors and ARBs act on systems other than the renin-angiotensin system. ACE inhibitors increase bradykinin concentrations. ARBs also increase bradykinin levels. (*However, the annoying dry cough and angioedema related to ACE do not occur with ARBs RTJ.)*

THE RAS LEFT VENTRICULAR HYPERTROPHY (LVH)

Evidence of early target organ damage in arterial hypertension, such as left ventricular hypertrophy, increases the risk of major cardiovascular events two-fold to five-fold.

In addition to the effects of increased afterload (elevated BP), the extent of vascular and cardiac damage, such as left ventricular hypertrophy, is greatly modulated by activity of the RAS.

In never-treated hypertensive people (eg, those with 24-h ambulatory BP load), high angiotensin-II concentrations are closely associated with high left ventricular mass.

The renin-angiotensin system aggravates left ventricular hypertrophy independently of, and in addition to, the blood pressure load imposed on the left ventricle in patients with primary hypertension

Of 5 antihypertension drugs recommended as first-line therapy, ARBs reduced LVH more than ACE inhibitors, and ACE inhibitors reduced LVH more than calcium blockers, beta-blockers, and diuretics. This effect was maintained at similar BP levels throughout 5 years.

It is not only a question of treatment duration or achieved BP. The choice of drug is also of clinical relevance for treatment of LVH.

Reduction of LVH translates into a reduced rate of cardiovascular complications, and improved prognosis. Reduction of LVH is a therapeutic goal in treatment of primary hypertension.

THE RAS AND ATRIAL FIBRILLATION (**AF**)

AF heightens the risk of cardiac mortality ~ 2-fold. It is an underlying cause of 15% of strokes.

On a population basis, hypertension is the most important cause of AF. In hypertensive persons, the most important (independent) risk factors for AF are age, left ventricular chamber diameter, and left ventricular mass.

Treatment of hypertension with ARBs has been reported to reduce incidence of AF by 20%.

In patients with congestive heart failure, both ACE and ARBs were reported to effectively reduce development of AF.

Proposed mechanisms for the effect of ACE inhibitors and ARBs in reducing risk of AF include: prevention of atrial dilatation and atrial fibrosis, slowing conduction velocity, lowering end-diastolic left ventricular pressure, modifying sympathetic tone, and direct anti-arrhythmic effects. In addition, blockade of the angiotensin-II cellular receptor by ARBs decreases inflammatory processes which may be important in development of AF.

“Thus, renin-angiotensin system blockage has emerged as a new preventive and therapeutic strategy for atrial fibrillation.”

THE RAS AND STROKE

The most crucial factor in stroke prevention is best possible BP control.

Meta-analyses suggest that ARBs (but possibly not ACE inhibitors) are effective in stroke prevention over and beyond BP control.

In hypertensive people with left ventricular hypertrophy, but without previous stroke, one study reported a 25% reduction in stroke with an ARB-based regimen compared with a beta-blocker-based regimen. Similar results were reported in patients with isolated systolic hypertension. In these trials control of BP with ARBs was much the same, suggesting the difference in stroke frequency could be attributed specifically to treatment with ARBs. In patients with previous stroke, another trial reported that re-occurrence of stroke was less frequent with ARB-based treatment than with calcium blocker therapy, at similar BP control.

The cerebro-protective effects of ARBs have emerged as a further important clinical means to address risk of ischemic stroke (in addition to the effect on lowering BP).

THE RAS AND ATHEROSCLEROSIS

Clinical and experimental evidence clearly indicate that activation of the RAS is related to the atherosclerosis cascade, vascular inflammation, generation of reactive oxygen species, and alterations in endothelial function.

Pro-inflammatory cytokines play a major part in the pathogenesis of atherosclerosis, and transformation of a stable plaque to a vulnerable plaque prone to rupture.

The chronic inflammatory response associated with atherosclerosis is modulated by the angiotensin-II receptor. Inhibition of the RAS can be a therapeutic means of reducing the response.

Angiotensin II induces oxidative stress. Blockade of the RAS could improve nitric oxide activity.

Clinical studies have reported that both peripheral and coronary endothelial dysfunction increase risk of cardiovascular events. Angiotensin II has been shown to initiate and sustain several mechanisms that contribute to impaired endothelial function.

Activation of the RAS promotes vasoconstriction and enhances migration and proliferation of vascular smooth muscle cells, increases synthesis of plasminogen activator inhibitor, and stimulates release of pro-inflammatory cytokines.

Several trials have reported that ACE inhibitors in high risk patients, and in low risk patients with stable coronary disease, reduce relative risk of cardiovascular events.

Blockade of the renin-angiotensin system has emerged as an obvious and attractive therapeutic target.

Whether ARBs produce effects similar to those of ACE inhibitors in atherosclerotic vascular disease is not yet answered.

THE RAS AND TYPE 2 DIABETES.

The best strategy is prevention. Measures to reduce disease burden for persons with established diabetes is also important. Blockade of the RAS intervenes at different stages of the disease process:

Blockade:

- Reduces insulin resistance.
- Increases perfusion of skeletal muscle and the pancreatic islet cells.

Reduces the loss of beta cell function due to the direct effect of angiotensin-II.

Clinical trials have reported the frequency of new onset type 2 diabetes can be reduced by ACE inhibitors and ARBs, in contrast to beta-blockers and diuretics which enhance risk.

In hypertensive patients at risk of developing type 2 diabetes—patients who have family history of type 2 diabetes, who have a body mass index greater than 30, and have impaired glucose tolerance—ARBs should be the first choice of antihypertensive treatment.

Complications of diabetes:

Blockade of the RAS reduced the frequency of diabetic nephropathy, and in high risk type 2 diabetic patients reduced cardiovascular mortality and morbidity.

Albuminuria and micro-albuminuria are markers of early nephropathy. Micro albuminuria predicts cardiovascular events in patients with diabetes, in those with hypertension, and in the general population. Blockade of the RAS prevents the onset of micro-albuminuria in diabetic patients and reduces proteinuria. ACE inhibitors have been reported to prevent onset of micro-albuminuria. ARBs have been reported to reduce occurrence of overt diabetic nephropathy.

ACE inhibitors and ARBs have been shown to reduce cardiovascular events in diabetic patients.

Blockade of the RAS in patients with advanced renal failure, especially diabetic renal disease, is safe and effective therapy. Some considerations favor ARBs over ACE inhibitors. ARBs may be more effective because of the high expression of chymase in the advanced diabetic kidney. As noted, this may lead to a highly activated RAS in local tissues. ACE inhibitors are not able to block formation of angiotensin II locally and thus are not effective. ARBs may be effective locally.

CONCLUSION

Improvement in the patient's cardiovascular risk by drugs which attenuate activity of the renin-angiotensin system is not related to BP reduction alone. Risk-reduction includes many other non-hemodynamic effects. "ARBs and ACE inhibitors are best proven interventions to reduce target organ damage in hypertension, atherosclerosis, and diabetes."

Lancet April 7, 2007; 369: 1208-19 Review article, first author Roland E Schmieder, University of Erlangen-Nuremberg, Germany

The review is more complex than I have indicated. The authors are certainly enthusiastic about benefits of RAS blockade. They seem to favor ARBs.

I believe much of the data they present in relation to development of type-2 diabetes remains to be more firmly established. "Effect of Ramipril (*an ACE inhibitor*) on the Incidence of Diabetes" (NEJM 2006; 355: 1608-18) reported results of treatment of RAS blockade in over 5000 patients with impaired fasting glucose on onset of type 2 diabetes. Ramipril (*Altace*) did not reduce the development of diabetes (primary endpoint)

compared with placebo. It did increase rate of regression to normoglycemia and lowered glucose levels after a 2-hour glucose load.

The article makes no comment on use of blockade in patients with congestive heart failure or post-myocardial infarction. Nor the importance of aldosterone interactions with the RAS.

For a more detailed consideration of the angiotensinogen - angiotensin-I – angiotensin-II - aldosterone system see Practical Pointers October 2006 [10-11]

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4-2 VALSARTAN IN A JAPANESE POPULATION WITH HYPERTENSION AND OTHER CARDIOVASCULAR DISEASE: The Jikei Heart Study

In Japan, hypertension is the most common cause of coronary heart disease (**CHD**) and heart failure (**HF**).

Angiotensin II has a well defined role in the pathogenesis of hypertensive left ventricular hypertrophy, stroke, CHD, and HF. Angiotensin II (**AT-II**) blockers were originally targeted at hypertension, but also benefit patients with a range of diseases, and reduce incidence of new-onset type-2 diabetes.

The investigators hypothesized that the AT-II blocker could yield additional protective benefits, compared with conventional treatment, and that the benefits would extend beyond those attributable to control of blood pressure.

Conclusion: Valsartan was associated with fewer cardiovascular events.

STUDY

1. Randomized, controlled trial entered over 3000 Japanese patients (mean age 65). All were undergoing conventional treatment for hypertension, CHD, HF, or a combination of these disorders.
2. Randomized to: 1) valsartan [40 to 160 mg daily], or 2) controls. Aimed to control BP in both groups to less than 130/80.

   Patients with hypertension who were randomized to valsartan, initially received a dose of 80 mg daily; adjusted to 40-160 mg. Patients with HF or CHD were started on 40 mg daily, and upgraded as tolerated.

   Controls were given either an increased dose of their existing treatment or an additional conventional treatment to achieve BP control. [1]

4. Primary outcome = composite of cardiovascular morbidity and mortality. Analysis by intention to treat. Follow-up for 3 years.

RESULTS

1. Mean BP was similar in the 2 groups during the 3 years. At the end of the trial, valsartan group BP was 132/77; control group 132/77.
2. Effects on all endpoints (rate per 1000 patient-years):

	Valsartan	Control	NNT
Composite endpoint	21 (6.0%)	35 (9.7%)	27
Stroke or TIA	8	11	
Angina pectoris	4	12	
New HF or exacerbation	4	8	
Dissecting aneurysm	0.5	2.3	
All cause mortality	6.5	6.3	

3. Mortality, myocardial infarction, and progression of renal disease did not differ between groups.

4. Adverse effects: Only 2.5% reported any adverse effect. No significant difference between groups.

DISCUSSION

1. In Japanese patients with cardiovascular disease, addition of valsartan to standard cardiovascular treatment reduced the incidence of heart and brain complications. The response was early and sustained.
2. Both groups showed a similar degree of BP control, achieving good control of similar magnitude. BP was not a major determinant of outcomes.
3. The cardiovascular diseases in this study population—heart failure, hypertension, and coronary heart disease—are all disorders in which activation of the renin-angiotensin-aldosterone system is thought to play a major part.
4. Some patients (~ 1/3) were receiving ACE inhibitors at baseline. They were continued in the valsartan group as well as in the placebo group. Thus, some patients in the valsartan group received two inhibitors of the renin-angiotensin system. The investigators had no proof that the renin-angiotensin system was adequately inhibited by the ACE inhibitors. But, this may have skewed results.
5. The study was not adequately powered to detect changes in all-cause mortality over 3 years.

CONCLUSION

The addition of valsartan to conventional treatment prevented more cardiovascular events than supplementation of conventional treatments. These results cannot be explained by a difference in BP control.

Lancet, April 28, 2007; 369: 1431-39 original investigation, first author Seibu Mochizuki, Jikei University, Tokyo, Japan.

1 Drugs at baseline, and continued during the trial, included calcium blockers, ACE inhibitors, beta-blockers, alpha–blockers, thiazides, statins, fibrates.

An editorial in this issue of Lancet, first author Jan A Staessen, University of Leuven, Belgium. comments: The editorialists congratulate the investigators. “We know how difficult it is to do a randomized trial in Japan.”

Nevertheless, one should not accept the main conclusions at face value. The design of the study did not protect against possible bias. By the editorialists’ calculation, BP during the first year of the study was significantly lower in the valsartan

group. At 6 months, the differences in BP averaged 2.1/2.1, and at 12 months, averaged 1.5/1.3. Small differences in the achieved BP could explain most of the differences in outcomes.

The trial was conducted in tertiary-care centers. The results cannot be extrapolated to general practice.

Two other comprehensive reviews do not support benefits of AT-II blockers ("sartan" drugs) beyond BP lowering.

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"How Acupuncture Works Is Not Readily Understood"

4-3 ACUPUNCTURE: A Clinical Conference

This clinical conference presents a 60-year old woman considering acupuncture for knee pain. She is basically healthy, energetic, and sophisticated. She now weighs 158 pounds and is 68 inches tall. (BMI = 24) Her knee pain started 8 years ago. She has experienced pain in both knees, which has been slowly progressive. X-ray confirmed osteoarthritis.

She has tried NSAIDs and chondroitin-glucosamine intermittently. But she does not like taking medicines.

She wants to know if acupuncture can help the pain, improve function, and stop progression of the arthritis. "I think there is a placebo effect. But that doesn't mean it doesn't work. I'm okay with that. If somebody told me it was just a 'placebo effect'—fine."

Data suggest that inflammation plays an important role in the pathophysiology of osteoarthritis, with respect to both production of pain and stiffness, and structural progression.

Non-pharmacological therapies range from patient education, social support, physical and occupational therapy, aerobic and resistive exercises, and weight loss. Meta-analysis reported that a wide range of muscle strengthening and aerobic exercises for hip and knee osteoarthritis (compared with non-exercise control groups) slightly reduced pain and improved function.

The limited ability of many commonly used interventions to reduce pain and improve function, combined with significant adverse effects of some drugs has led many patients to try therapies outside the mainstream of medicine. A National Health Survey reported that 41% of respondents with arthritis had used some form of complementary-alternative medicine: 21% used biologically based therapies; 21% mind/body therapies, and 1% used acupuncture. "High-quality evidence evaluating CAM has been scarce."

The discussant focuses on the role of acupuncture relative to other treatments for the pain of osteoarthritis.

"The perception of acupuncture as a legitimate medical intervention expanded when the National Institutes of Health and the FDA held consensus developmental and technological assessment conferences (1998) that resulted in recommendations on the potential use of acupuncture, in particular for pain-related conditions, as well as post-operative and chemotherapy-induced nausea and vomiting and when the FDA reclassified acupuncture needles from investigational devices to medical devices."

Surveys of rheumatologists and pain specialists reported that 56% to 84% considered acupuncture a legitimate medical practice.

From the Western medical viewpoint, how acupuncture works is not readily understood. Research is elucidating two theories: 1) activation of a gate control system, and 2) stimulation of the release of neurochemicals in the central nervous system. Animal studies suggest that acupuncture stimulates peripheral nerves that send impulses to the spinal cord, the midbrain, and hypothalamic-pituitary system. This leads to release of endorphins and cortisol, causing analgesia. Acupuncture also appears to activate descending pain-inhibiting pathways and to deactivate limbic structures that are the mechanisms involved in the sensory and affective components of pain. Locally, acupuncture appears to induce vasodilation, and inhibit release of histamine and prostaglandins.

What is the evidence for acupuncture for osteoarthritis of the knee?

The discussant cites 4 randomized trials (acupuncture vs sham acupuncture). All used the WOMAC index pain scale (0 to 20) and function scale (0 to 68) for measuring outcomes. For 2 trials, acupuncture showed (statistically) significant, but small benefits, (1 point and 2.5 points) short-term. One RTC showed larger benefits (5 and 17 points improvement short term). One trial showed no improvement. "The definition of appropriate sham acupuncture is still not resolved."

The benefits of some of the other knee osteoarthritis treatments (eg, intra-articular corticosteroids relative to placebo) are larger than the effects of acupuncture (relative to sham acupuncture).

There are a wide variety of schools of acupuncture, ranging from traditional Chinese methods to Western styles. Japanese and Chinese acupuncture are very different. As a consequence, there are many distinct styles of practice. Points of acupuncture vary. Points chosen for treatment vary from treatment to treatment. Variations include depth of needle penetration, the number of needles used, diameter and length of the needles, and the length of time needles are left in place. Different types of needle stimulation are used—manual, heat, electrical. Recent trials administered acupuncture 1 to 2 times weekly for a minimum of 8 weeks.

Safety of acupuncture:

Infections were the most common adverse effects in the past.(especially hepatitis). No cases have been reported since 1988 when US certification requirements for clean needle technology and use of disposable needles were introduced. Bruising may occur. Patients should inform the practitioner if they are taking anticoagulants.

Choosing a practitioner:

Most practitioners in the USA are non-physicians. Many have been trained at the 47 accredited schools in this country (The Accreditation Commission for Acupuncture and Oriental Medicine). Regulation is on a state-to-state basis. Physician-acupuncturists who are members of The American Academy of Medical Acupuncture have had 220 hours of formal training and 2 years of clinical experience.

Communication between the patient's physician and the patient's acupuncturist is important. Acupuncture should be a part of a multidisciplinary approach to osteoarthritis. If acupuncturists use other modalities (eg, herbs) adverse effects and potential interactions with prescription and over-the-counter drugs should be assessed.

Costs: Typically range from $65 to $125 per session. There is no standard for insurance coverage. Medicare and Medicaid do not reimburse.

Most clinicians use multidisciplinary approaches to the management of osteoarthritis, recognizing that most available treatments have small effects. Different treatments used concurrently may provide incremental improvements. Adding acupuncture may increase costs Some patients respond; some do not.

Recommendations by the discussant for the patient:. "She is interested in non-pharmacological approaches to pain management. I would recommend she try a course of acupuncture treatments. But first, she may want to check if her insurance company now provides coverage. I expect acupuncture will provide relief in the short run, but I have no good answers for the long-term impact." He also suggests an exercise program to strengthen her quadriceps. And that she take acetaminophen or NSAIDs regularly. Although evidence of benefit is weak, she should consider taking glucosamine-chondroitin on a continuous basis.

Clinical improvement with respect to pain can be due to many factors: natural history and regression to the mean, specific effects of treatment, non-specific effects of treatment including physician- and patient-expectations, beliefs, and interactions. "These non-specific or so-called placebo effects can play a role in all interactions between patient and provider, and are found with drugs, surgery, psychotherapy, medical devices, diagnostic tests, and acupuncture."

Cultural factors, which include expectations and beliefs, are extremely important influences on the outcomes of many treatments, acupuncture included.

JAMA April 10, 2007; 297: 1697-1707 "Clinical Crossroads" conference at Anesthesia Grand Rounds held at Beth Israel Deaconess Medical Center, Boston Ma, discussed by Brian Berman, University of Maryland School of Medicine, Baltimore.

Dr. Berman performs acupuncture as part of his clinical practice.

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Hormones Remain A Reasonable Option For The Short-Term Treatment Of Menopausal Symptoms.

4-4 POSTMENOPAUSAL HORMONE THERAPY AND RISK OF CARDIOVASCULAR DISEASE BY AGE AND YEARS SINCE MENOPAUSE

The Women's Health Initiative (**WHI**), a large observational study (2003), reported that conjugated equine estrogens (**CEE**) conferred a slight *protection* against coronary heart disease (**CHD**) [hazard ratio = 0.95]. And combined conjugated equine estrogens + medroxyprogesterone acetate (**CEE + MPA**) *increased* risk

(HR = 1.24).

Subgroup analysis of two WHI trials suggested a non-significant *reduction* in risk of CHD in women age 50-59 who were taking CEE-alone. Risk was also reduced in women with less than 10 years since menopause taking CEE + MPA. Risk of stroke did *not* appear to be reduced with either.

Observational studies of hormone replacement therapy (**HRT**) have, in the past, overestimated benefits. This was likely due to confounding selection biases. Another source of discrepancy might be the timing of initiation of HRT in relation to the underlying state of the vasculature.

Some investigators have hypothesized that estrogen may delay the onset of the earliest stages of atherosclerosis (which are more likely in younger women), but may be ineffective or even trigger cardiovascular events in the presence of existing advanced atherosclerotic lesions (such as those found in older women). There may be a potential window of opportunity for hormone therapy to reduce cardiovascular disease.

This study (a secondary analysis) explored whether the effects of hormone therapy on risk of cardiovascular disease vary by age or years since menopause.

Conclusion: Women who initiated HRT closer to menopause tended to have reduced risk of CHD. Risk increased in women more distant from menopause. The risk of stroke was elevated regardless of years since menopause.

STUDY

1. The WHI trials enrolled over 27 000 predominantly healthy postmenopausal women aged 50 to 79.
   Over 10 000 had undergone hysterectomy and received CEE-alone (0.625 CEE-alone vs placebo).
   Over 16 000 received CEE + MPA (CEE 0.625 mg + MPA 2.5 mg) vs placebo.
2. Main outcome measure = effect of HRT on coronary heart disease (**CHD**) and stroke across categories of age and years since menopause.

RESULTS

1. CEE-alone vs placebo:
   A. Absolute number of *CHD events* by years since menopause at baseline:

	CEE-alone	Placebo
< 10 years	8 (n = 826)	16 (n = 817)
10 – 20 years	47 (n = 1436)	50 (n = 1500
> 20 years	117 (n = 2231)	111 (n = 2319)

   B. Absolute number of *stroke* by years since menopause at baseline:

	CEE-alone	Placebo
< 10 years	17	8
10 – 20 years	43	30

> 20 years	86	72

C. No indication that it is a risk factor for CHD at earlier ages. Risk increases at age 70
Associated with increased risk of stroke at all ages.

2. CEE +MPA vs placebo:

A. Absolute number of *CHD events* by years since menopause:

	CEE + MPA	Placebo
< 10 years	31 (n = 2782)	35 (n = 2712)
10 – 20 years	66 (n= 3047)	53 (n = 2994)
> 20 years	77 (n = 1850)	47 (n = 1803)

B. Absolute number of *stroke* by years since menopause:

	CEE + MPA	Placebo
< 10 years	24	15
10 – 20 years	57	49
> 20 years	56	41

(Not statistically significant for any group.)

C. No indication that it is a risk factor CHD at earlier ages. Risk increases after 10 years.
Associated with increased risk of stroke at all ages.

3. Absolute differences were very small. The NNT to benefit or harm were very large.

DISCUSSION

1. Although not statistically significant, these secondary analyses suggest that the effect of hormones on CHD may be modified by years since menopause, with the highest risk in older women (> 70).
2. CEE-alone taken within 10-20 years of menopause was not related to increased risk of CHD. It was associated with a small increase in risk after 20 years.
3. CEE-alone was related to increased risk of stroke 10-20 years after menopause.
3. CEE + MPA did not appear to increase risk of CHD within the first 10 years. Increased risk thereafter. CEE + MPA was associated with increased risk of stroke at all ages.
4. Estrogen may have dual and opposing actions, retarding the earlier stages of atherosclerosis through beneficial effects on endothelial function and blood lipids, but triggering acute events in the presence of advanced lesions through pro-coagulant and inflammatory mechanisms.
5. The low or absent excess risks of CHD in women less than 10 years since menopause may be somewhat reassuring to women considering the use of HRT in the first few years after menopause.
6. At a minimum, screening and treatment of risk factors for stroke would be advisable before considering HRT.
7. Non-adherence may have affected the results. At the end of the trials, 54% of the CEE patients and 42%

of the CEE + MPA patients were no longer taking the hormones. These results are therefore derived from relatively short durations of treatment, but the average of 4 to 5 years of receiving treatment in the trials is longer than most women would need for treatment of vasomotor symptoms.

8. The absence of excess absolute risk of CHD, and the suggestion of reduced mortality in younger women offers some reassurance that hormones remain a reasonable option for the short-term treatment of menopausal symptoms.
9. For CEE + MPA, the risk of *breast cancer* also needs to be considered. In women less than 10 years after menopause, there were 72 (0.32%) cases compared with 57 (0.28%) cases while taking placebo.

CONCLUSION

Women who initiated HRT closer to menopause tended to have reduced risk of CHD. Risk increased in women more distant from menopause. The risk of stroke was elevated regardless of years since menopause.

JAMA April 4, 2007; 297: 1465-77 Original investigation by the Women's Health Initiative, first author Jaques E Rossouw, National Heart, Lung, and Blood Institute, Bethesda MD

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"Under-Prescribing Of Opioids Remains A Major Barrier To Effective Pain Control"

4-5 MORPHINE KILLS THE PAIN, NOT THE PATIENT

Over 20 years ago, the work "opiophobia" was coined to describe the analgesic-prescribing habits of physicians. Then, in 1987, the WHO published its analgesic ladder, which identified morphine as the most effective analgesic for cancer pain, and effectively made a nation's per-capita consumption of morphine an indication of the extent to which its citizens have access to pain relief and palliative care.

Global morphine consumption has increased by over 10 times in the past 20 years.

Public and professional anxieties about the effects of morphine continue to hinder adequate access to analgesia. The best known fact about morphine among the public is that it can be addictive. (In fact, the risk of iatrogenic addiction is under 0.1%.) For physicians, the second best known fact is that morphine can precipitate respiratory depression.

The media take it as an accepted fact that everyday medical practice for pain control entails the use of increasing morphine doses until the patient dies as a result. This is not surprising. "This is a taint to which palliative-care physicians have been obliged to become accustomed."

A recent study from the US National Hospice Outcomes Project compared opioid use and survival at the end of life. Hospice inpatients (n = 725) with end-stage cancer, lung disease, or heart disease were followed up to death. The length of stay was *positively* correlated with the maximum daily opioid dose received, even when that dose exceeded 15 times the average for patients in the UK. Neither absolute dose nor change in dose was linked to shortened survival.

Only the morphine-naive patient is at significant risk of respiratory depression. Patients who are given the incremental dose-titration practiced in palliative care centers are not at such risk.

"A physician who truly is killing his or her patient in the name of pain relief is not merciful, just incompetent."

Under-prescribing of opioids remains a major barrier to effective pain control. "Physicians should be encouraged to use opioids effectively to relieve suffering at the end of life."

Lancet, April 21, 2007; 369: 1325-26 Comment by Nigel P Sykes, St Christopher's Hospice, London, UK

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"It Would Seem That Becoming Slightly Overweight May Not Be So Bad."

4-6 THE EFFECT OF OBESITY ON DISABILITY VS MORTALITY IN OLDER AMERICANS

There is a strong relationship between obesity, usually assessed by body mass index (BMI[1]) and increased risk of death.

A consistent and puzzling finding is that the effect of obesity on mortality may be diminished among older persons.

A study in NEJM in 1998[2] of 300 000 participants in the American Cancer Society Prevention Study reported relations between BMIs and mortality. For subjects younger than age 55, BMIs lower than 20 were associated with the lowest mortality; BMIs in the mid 20s were associated with a 20% increase in all-cause and 50% increase in cardiovascular mortality. In subjects over age 75, BMIs associated with the *lowest* mortality were in the range of 27 to 29 (defined as overweight). And that the increase in risk of mortality associated with each unit-increase in BMI above the optimal values declined sharply with age. *(Ie, in the elderly, increasing weight was not as detrimental as it was in younger persons. RTJ*)

The finding that BMIs in the near-obese or obese range are associated with optimal survival among older persons has been reproduced in several well –conducted studies. This association is not greatly affected by attempts to control for reversed causation, whereby underlying poor health produces lower BMIs and increases mortality. This finding has led to calls for increasing the recommended BMI from its current range of 18.5 to less than 25, to higher values in older people.

There are many important measures of health in addition to mortality. It may be preferable to base desirable weight on other outcomes such as disability or risk of disease. The magnitude of the association of obesity with disability may be comparable to, or greater than, the association between obesity and mortality.

This study (Established Populations for Epidemiological Studies of the Elderly) examined the association between BMI and subsequent mortality and incident disability during 7 years, and estimated the effect of BMI on life expectancy and disability-free life expectancy in initially non-disabled persons. The investigators

hypothesized that a higher BMI in persons over age 65 would be associated with greater disability, greater mortality, and lower disability-free life expectancy.

Conclusion: For the elderly, higher BMIs may not be as detrimental as they are in younger persons.

STUDY

1. Entered over 12 500 persons age 65 and older (mean = 72) between 1982 and 1993. None were disabled. None had limitations in activities of daily living (**ADL**).
2. Grouped BMI according to NIH obesity standards: < 18.5 underweight; 18-5-24.9 normal weight; 25 to 29.9 overweight; 30 to 34.9 obesity category I; 35 to 39.9 obesity category II; and 40 and over extreme obesity.
3. Estimated hazard ratios (HRs) for subsequent mortality and disability.

RESULTS

1. Relation between BMIs and <u>mortality</u>:
   - BMIs associated with the minimum hazard of mortality were between 25.1 and 29.9 (overweight).
   - Subjects with BMIs 25 to 18.5 ("normal" weight) experienced a higher mortality.
   - For BMIs lower than 18.5 (underweight), hazard rations continued to rise sharply.
   - For subjects with BMI 30 to 35, hazard ratio of death rose gradually up to ~ 1.3 for BMI of 35.
   - There was a fairly steep rise in mortality associated with lower BMIs and a more gradual increase in hazard associated with higher BMIs.
   - There was a difference between men and women: For men, the total life expectancy was greatest with BMIs between 25 and 29.9. For women it was between 30 and 34.9 (obese).
2. Relation between BMIs and <u>disability</u>:
   - The lowest point-hazard ratio for disability associated with ADL was a BMI of 24.
   - Hazard ratio for disability rose to ~ 1.2 as BMI rose to 27.
   - Hazard ratio for disability rose to ~ 1.2 as BMI fell to 22-23
   - There was a fairly steep increase in the hazard of disability associated with lower and higher BMIs.
3. <u>Disability-free life expectancy:</u>
   - Disability-free life expectancy was greatest among both men and women with a BMI of 25 to 29.9 (overweight).
   - The estimated total life expectancy that will be disability-free fell sharply for subjects with BMI 30 and higher (obese).

DISCUSSION

1. Comorbidity and smoking status and other risk factors obscure the association between obesity and mortality.

This study adjusted for comorbidity by excluding current smokers, and by excluding subjects who died during the first 2 years of follow-up

2. The association between elevated BMI and mortality may be attenuated by selective survival. Elevated BMI is clearly associated with increased mortality at younger ages. It is possible that persons susceptible to increased early mortality associated with elevated BMI die at younger ages, weakening the observed relationship at older ages.
3. Higher BMIs may have a protective effect in older ages that is less important at younger ages. This protective effect might counterbalance the known adverse consequences of obesity on survival. Examples of a protective effect include the decreased risk of hip fractures and increased ability to tolerate periods of low caloric intake associated with acute illness.
4. Various interpretations may lead to different or conflicting recommendations regarding the ideal BMIs in older persons. “Our results suggest that the association between BMI and mortality is only one factor in determining optimal BMIs values for older adults.” Loss of independence is one of the most feared outcomes experienced by older individuals, and is a major contributor to poor quality of life.
5. The association between elevated BMIs and subsequent disability provides evidence that obesity (BMIs > 30) in older populations is associated with substantial increase in risk of poor health outcomes.

CONCLUSION

“Assessments of the effect of obesity on health of older Americans should account for mortality and incidence of disability.”

Disability-free life expectancy was greatest among subjects with a BMI of 25 to 29.9 (overweight).

Archives Intern Med April 23, 2007; 167: 774-80 Original investigation, first author Soham Al Snih, University of Texas Medical Branch, Galveston.

1 BMI = weight in kg divided by height in meters squared.

2 “The effect of age on the association between body mass index and mortality” NEJM 1998;338: 1-7

An editorial in this issue of Archives, first author Luigi Ferrucci, National Institute on Aging, Baltimore MD, comments:

Interestingly, for both men and women, disability-free life expectancy was greatest among the overweight (BMI 25 to 30). “At the individual level, considering the trade-off between total and disability-free life expectancy, it would seem that becoming slightly overweight may not be so bad.”

Recent analyses suggest that in older persons, waist circumference may be a better predictor of mortality than BMI. It is not known whether the relationship between waist circumference and mortality differs in different age groups.

Only about half of the study cohort survived to age 65. Because of the effect of obesity on mortality tends to decline with age, those available to participate in a study of older persons constitute “healthy survivors”.

The editorialist comments that adipose tissue operates as both an endocrine organ and active metabolic tissue.

Adipocytes are cell-to-cell signaling proteins secreted by adipose tissue. They up-regulate systemic inflammation and cause insulin resistance. (Inflammation is an independent risk factor for disability.)

Adiponectins are protein hormones which are exclusively secreted from adipose tissue. They are abundant in plasma. They modulate glucose regulation and fatty acid catabolism, and play a role in type-2 diabetes, obesity, and atherosclerosis. Levels are *inversely* correlated with BMI. (Ie, as BMI rises, levels of adiponectins fall.). Supplementation with adiponectins improves insulin control, blood glucose levels, and triglyceride levels. (*Data in part accessed by me from Google RTJ*)

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"No Simple Recommendation Applies To All Women In Their 40s"

4-7 BREAST CANCER SCREENING FOR WOMEN IN THEIR 40s: Moving from Controversy about Data to Helping Individual Women

Women in the USA now generally expect that screening should begin at age 40.

The editorialist simplifies the results of screening women for breast cancer (**BC**) starting at age 40. For every 10 000 women screened regularly, 6 might benefit through decreased risk of death due to BC. This modest benefit requires multiple screening examinations and follow-up for all 10 000 for more than a decade. Thus, 9994 women receive no mortality benefit because most women will not develop BC, and some will have cancer detected too late for a cure. Women in their 40s grossly overestimate their risk of dying from BC within 10 years, and also overestimate the absolute risk reduction associated with screening mammography. Clinicians may also over-estimate risk.

What are the potential harms of screening? False positive results are more common in younger women. Among those starting screening at age 40, about half might receive at least one false positive result over a decade of annual screening. Further diagnostic procedures follow, with about 2000 women eventually undergoing a biopsy. Anxiety is increased. Costs are considerable.

"In the field of breast cancer screening, the actual practice of evidence-based medicine becomes deeply entangled with social, political, and economic forces." A National Institutes of Health consensus panel in 1997 reported that data available at the time were insufficient to make a recommendation for or against routine screening women in their 40s. Prominent physician leaders stated they were shocked, and called the group fraudulent. The US Senate voted 98 to 0 in favor of screening women in this age group.

Another complicating factor is the current context of medical malpractice lawsuits. Failure or delay in BC diagnosis has been the most common issue in medical malpractice claims against physicians. "We are concerned that breast cancer screening practice is being shaped more by potential legal ramifications than by evidence and patient choice."

"In the face of continuing controversy about evidence, our priority now should be to help women make informed decisions." "No simple recommendation applies to all women in their 40s. We must learn to become comfortable with using the art of medicine to translate the existing science. We must listen carefully to our patient and communicate honestly the benefits and limitations of our imperfect tests."

Annals Int Med April 3, 2007; 146: 529-31 Editorial, first author Joanne G Elmore, University of Washington, Seattle.

Three articles presenting more details appear in this issue of Annals:

"The Long-Term Effects of False-Positive Mammograms" (pp 502-10)

"Screening Mammography in Women 40 to 49 Years of Age: A Clinical Practice Guideline" (pp 511-15)

"Screening Mammography in Women 40 to 49 Years of Age: A Systematic Review" (pp 516-26)

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The Two-Drug Tablet Provided More Favorable Clinical Benefits

4-8 SUMATRIPTAN-NAPROXIN FOR ACUTE TREATMENT OF MIGRAINE

Triptans for treatment of migraine were introduced 15 years ago. They represent a significant advance in migraine headache (**HA**) therapy. However, therapeutic shortfalls remain. Some patients do not achieve headache relief by 2 hours, and recurrence of HA within 24 hours is common.

"None of the currently available monotherapeutic agents provides broad coverage of the multiple pathogenic processes in migraine, which is thought to involve multiple neural pathways that appear to be sequentially activated and sensitized as a migraine attack develops." Multi-mechanism-targeted therapy may confer advantages over monotherapy.

This study compared efficacy and safety of a two-drug, fixed-dose tablet containing a triptan and naproxen vs each as monotherapy, and vs placebo.

Conclusion: For acute treatment of migraine, the two-drug tablet provided more favorable clinical benefits "with an acceptable[1] and well tolerated adverse effect profile".

STUDY

1. Multicenter study entered over 2900 patients (age 18-65; mean = 40; the great majority female) with migraine. All had a history of migraine (mostly without aura) for at least 6 months, and had 2 to 6 moderate-to-severe episodes monthly.
2. Randomized double-blind to:
   1) A single tablet containing sumatriptan (*Imitrex*: GlaxoSmithKline; 85 mg) and naproxen (Generic; *Naprosyn*; Roche; 500 mg)
   2) Sumatriptan alone (Fast-disintegrating, rapid-release)
   3) Naproxen alone
   4) Placebo
3. To be used after onset of a migraine with moderate to severe pain. A second dose was not permitted.
4. Primary outcomes: % of patients with headache relief at 2 hours; absence of photophobia and phonophobia; absence of nausea. And % of patients with sustained pain-free response.

5. Patients were permitted to take rescue medication beginning at 2 hours.

RESULTS

1. At 2 hours:	S + N (%)	Placebo (%)	A D[a] (%)	NNT[b]
HA relief	61	28	33	3
Absence of photophobia	54	28	26	4
Absence of phonophobia	57	36	21	5
Absence of nausea	68	65	Not significant	

2. Two-hour to 24-hour:	S + N	S alone	N alone	Placebo	A D[c]	NNT
Sustained pain-free	24%	15%	10%	8%	16%	6
3. Recurrence in 24 hours	23%	35%	38%	55%	32%	3

a = absolute difference b = number needed to treat to benefit one patient c = S + N vs placebo

4. Sustained relief of nausea and vomiting greater with S + N (NNT = 5).

5. Use of rescue medication was less frequent in the S + N group.

6. Clinical safety:

At least one adverse event	S + N	S alone	N alone	Placebo
(regardless of suspected cause)	27%	26%	13%	11%

Adverse events: dizziness, somnolence, paresthesias, nausea, dry mouth—all from 2% to 5%

No statistically significant differences in overall adverse events between S + N, N-alone, and S-alone

One serious event probably attributed to S-alone: hospitalization for heart palpitations in a 58-year old woman.

DISCUSSION

1. Development of the tablet was motivated by the rationale that concurrent use of two agents with complementary anti-migraine mechanisms might confer additive benefit relative to either alone.

2. Triptans and NSAIDs target distinct aspects of the vascular and inflammatory processes hypothesized to underlie migraine. Triptans inhibit vasodilation, inhibit release of inflammatory mediators from the trigeminal nerve, and may interrupt transmission between peripheral and central neurons thereby interrupting activation of central pathways. NSAIDs inhibit synthesis of prostaglandins and may mitigate meningeal inflammation while preventing central sensitization. The combination would hypothetically alter both peripheral activation of central pathways and development of central sensitization.

3. With concomitant administration of S + N, sumatriptan is absorbed relatively quickly. Time to maximum concentration of naproxen is delayed, and its maximum plasma concentration is reduced by about 25%.

6. Sumatriptan has been reported to delay gastric emptying.

7.. S + N was associated with about twice the incidence of any adverse event as placebo (dizziness, paresthesias,

somnolence, nausea, dry mouth; none serious). No special adverse event or group of adverse events accounted for this difference. The nature of adverse events following S + N did not differ from events associated with S monotherapy, or N monotherapy in previous trials.

CONCLUSION

S +N as a single tablet for acute migraine resulted in more favorable clinical benefits than either monotherapy with S, monotherapy with N, or with placebo. .

JAMA April 4, 2007; 297: 1443-54 Original investigation, first author Jan Lewis Brandes, Nashville Neuroscience Group, Nashville, TN.

1 "Acceptable" as applied to adverse events amuses me. "Acceptable" to whom? The patient?

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Physicians Do Not Often Consider Patients' Costs

4-9 PHYSICIAN CONSIDERATION OF PATIENTS' OUT-OF-POCKET COSTS IN MAKING COMMON CLINICAL DECISIONS

Patients face growing cost pressures. Insurance limits coverage for specific services. Cost sharing is meant to offset payer expenditures by shifting responsibility for costs of care to patients, and creating incentives for them to reduce health care demand. Higher deductibles also increase costs to patients.

Physicians' decisions affect how 90% of every health dollar is spent. Whether increased cost-sharing can effectively control health care spending depends on whether patients and physicians can together consider costs during clinical decision-making.

Studies suggest that patients confronted with higher out-of-pocket costs (**O-O-P costs**) often chose to forego physician visits or care that has been recommended by a physician (eg, filling a prescription; obtaining a recommended test).

Physicians serve as patients' agents, and increasingly are called on to deliver patient-centered care.

Physicians do not often consider issues about O-O-P costs.

Physicians sensitivity to patients' O-O-P costs might vary considerably based on the amount of clinical discretion allowed within accepted practice standards; the magnitude of economic burdens the patient might face; and how invested physicians are in patient satisfaction.

This study analyzed data on how frequently physicians considered their patients' O-O-P costs. And assessed the physician characteristics associated with this practice. Does consideration of O-O-P costs affect clinical decision making?

STUDY

1. The Community Tracking Study of Physician Survey, a nationally representative survey, was conducted

4 times since 1996. This analysis of over 6600 respondents was based on the 2004-05 survey. Primary care physicians were over-represented

2. Asked: How often do you consider an insured patient's O-O-P costs when:
   1) Prescribing a generic over a brand-name drug?
   2) Deciding the types of tests to recommend ?
   3) Choosing between inpatient and outpatient care settings?

RESULTS

1. O-O-P costs in prescribing drugs: 78% of physicians reported regularly (always or usually) taking patients' O-O-P costs into account when prescribing generic over brand-name drugs. Primary care physicians were more likely than specialists to do so.
2. O-O-P costs in selecting care settings and diagnostic tests: 51% reported considering O-O-P costs in choosing outpatient vs inpatient care settings. 40% did so in selecting diagnostic tests. Medical specialists were less likely to do so. Physicians in solo or 2-person practices were more likely to consider O-O-P costs when choosing diagnostic tests and care settings.
3. Physicians treating patients of lower socio-economic status tended to be more likely to consider costs, as were physicians who had more patients receiving Medicaid.

DISCUSSION

1. As insurers and employers seek to control health costs, patient cost-sharing is likely to remain a prominent tool for influencing healthcare utilization. How well this works depends on physicians' sensitivity to their patients' O-O-P costs.
2. Despite increases in cost-sharing burdens, most physicians do not take them into account when making care recommendations surrounding diagnostic tests and care settings. Physicians may prioritize other considerations (accuracy of the test; ease of scheduling) above patients' O-O-P costs.
3. Physicians and patients are not likely to have ready access to detailed cost data.
4. Specialists were more resistant to consideration of O-O-P costs then primary care clinicians. They may be less sensitive to patients' economic burdens, perhaps because of less continuous care relationships, and less knowledge about patients' social and economic status. Specialists are more likely to perform many types of diagnostic procedures. Their patients may have more severe illnesses. "These specialty differences compound concerns that cost-sharing will have limited effects on the use of more expensive medical services."
5. Lower-income Americans are more likely than the wealthier to have high O-O-P health care spending burdens relative to their family incomes. REDO

CONCLUSION

Physicians do not routinely consider patients costs when making decisions about prescribed drugs, and especially about costs of tests and outpatient vs inpatient care.

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