PRACTICAL POINTERS

FOR
PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

SEPTEMBER 2003

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

PUBLISHED BY PRACTICAL POINTERS, INC.
EDITED BY RICHARD T. JAMES JR. MD
400 AVINGER LANE, SUITE 203
DAVIDSON NC 28036 US
www.practicalpointers.org rjames6556@aol.com

SEPTEMBER 2003

HIGLIGHTS AND EDITORIAL COMMENTS

9-1 EFFECT OF INTENSITY OF ORAL ANTICOAGULATION ON STROKE SEVERITY AND MORTALITY IN ATRIAL FIBRILLATION

Emboli of atrial origin are larger than average. The brain infarcts they produce are more disabling and lethal.

Among patients with non-valvular AF, the degree of anticoagulation at admission for stroke was associated with risk of disability and death. Anticoagulation that resulted in an INR of 2.0 or greater reduced frequency and severity of ischemic stroke and risk of death. This is evidence against INR targets below 2.0

Risk of hemorrhagic stroke did not increase until INR was 4.0 or above.

INR below 2.0 and aspirin protect against stroke less effectively than INR 2.0 to 3.0, but are superior to use of no anticoagulant. Aspirin is adequate prophylaxis in patients considered at low risk for thromboembolic stroke. Eventually almost all patients with AF will become high risk due to age and co-morbidity. As age progresses, risk of bleeding from warfarin increases. This dilemma must be solved on an individual basis. Patients accepting warfarin must be carefully controlled at a stable INR around 2.5.

"Our results provide further support for anticoagulation to achieve an INR of 2.0 or greater (eg, 2.5) in patients with non-valvular atrial fibrillation."

9-2 ORAL XIMELAGATRAN FOR SECONDARY PROPHYLAXIS AFTER MYOCARDIAL INFARCTION

In patients with a recent MI, long term treatment with ximelagatran, combined with aspirin, was more effective than aspirin alone in reducing frequency of major cardiovascular events. [NNT (for 6 months to benefit one) = 33]

Ximelagatran is the first of a new class of *oral direct-thrombin inhibitors* under investigation. It is rapidly metabolized to its active form, melagatran. It is stable over time. Its metabolism is unaffected by age, sex, body weight, or ethnic origin. It is not affected by the hepatic cytochrome P450 enzyme system, thus providing a low potential for drug-drug interactions. There are no relevant food or alcohol interactions. "Melagatran's pharmacokinetics are unchanged and the pharmacodynamic properties show only minor additive effects when oral ximelagatran and acetylsalicylic acid are given concomitantly."

Ximelagatran has undergone extensive assessment in patients with venous thromboembolism and atrial fibrillation. It has a rapid onset of action, achieves a peak level within 2 hours, and has a half-life of 4 hours. It is administered twice daily. There is no need of monitoring and dose adjustments. (*Monitoring of liver and kidney function is required. RTJ*) Ximelagatran is primarily excreted by the kidney. Data on patients with kidney dysfunction are limited.

With the 24 mg BID dose, the bleeding rate was low, and high concentrations of alanine amino transferase occurred less frequently (7%).

"It is good news that the more than half century wait of new and improved oral antithrombotics finally appears to be ending."

9-3 EFFICACY OF PERINDOPRIL IN REDUCTION OF CARDIOVASCULAR EVENTS AMONG PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Among patients with *stable* CAD without apparent heart failure, the angiotensin converting enzyme

inhibitor, perindopril (*Aceon*) improved outcomes. This was in addition to use of other preventive drugs. [NNT(4 years to benefit one) = 50]

ACE inhibitors have been shown to have the broadest impact of any drugs in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, post myocardial infarction left ventricular dysfunction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks.

As long-term therapy, perindopril is expensive. It has not been compared with less expensive ACE inhibitors (eg, enalapril) which may be just as effective.

ACE inhibition is underused in primary care practice.

9-4 LIFETIME RISK OF CORONARY HEART DISEASE BY CHOLESTEROL LEVELS AT SELECTED AGES.

For persons *of all ages*, lifetime risk of CHD increases as total cholesterol levels rise from under 200 to over 240. This supports the important role of cholesterol screening at all ages.

This article is of considerable clinical importance even though it provided no outcomes from lifestyle or drug interventions. Patients, old and young, now have a reasonable prediction of lifetime risk according to total cholesterol levels. (And cholesterol subfractions.) Old, and young should be screened periodically. The data may convince some younger persons to intervene to reduce their lifetime risk

Guidelines suggest lipid screening begin at age 20.

9-5 SOCIAL ANXIETY DISORDER

The hallmark of social anxiety disorder (SAD) is extreme and persistent fear of embarrassment and humiliation. People with SAD (also known as social phobia) avoid participating in social and public activities such as public speaking, social gatherings, and meetings. The intense symptoms of SAD interfere with functioning and cause marked distress.

It is the third most prevalent psychiatric disorder in the USA. Paroxitine and sertraline are effective drug therapy.

SAD can be differentiated from panic disorder by its consistent relation to social issues.

Less severe, and more common symptoms can benefit from beta-blockers.

9-6 EFFECTS OF CANDESARTAN ON MORTALITY AND MORBIDITY IN PATIENTS WITH CHRONIC HEART FAILURE

ACE inhibitors have been shown to have the broadest impact of any drug in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, left ventricular dysfunction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks.

Candesartan, blocks angiotensin II at the cellular level. Given to patients with heart failure in *addition* to other drugs (including ACE inhibitors) it was associated with reduced cardiovascular deaths and hospital admissions for heart failure.

Reducing angiotensin II levels is a basic therapy in cardiovascular disease. ACE inhibitors have been the standard. Addition of an angiotensin II blocker may benefit slightly. They should be used when the patients cannot tolerate ACE inhibitor.

9-7 POLYPHARMACY AND COMORBIDITY IN HEART FAILURE

Primary care clinicians are responsible for reviewing medication lists with a goal of eliminating medications that are not known to provide clear benefits. Little evidence is available to guide polypharmacy in patients with heart failure and other common conditions

Too many patients, especially the elderly, are taking too many drugs.

Primary care clinicians should insist that their patients bring to the office for review all medications they use, including those prescribed by other physicians, standard drugs bought over the counter, and herbal nostrums used as "alternative" medicines. This seems difficult for patients to do, but is most important.

9-8 ABILITY OF EXERCISE TESTING TO PREDICT CARDIOVASCULAR AND ALL-CAUSE DEATH IN ASYMPTOMATIC WOMEN: A 20-YEAR FOLLOW-UP OF THE LIPID RESEARCH CLINICS PREVALENCE STUDY

Exercise capacity and heart rate responses were strong, graded, and independent predictors of cardiovascular and all-cause mortality. Not achieving target heart rate and slow return of the rapid heart rate induced by exercise toward normal predicted future mortality in younger women.

ST segment depression, while predictive in men, had no value in women.

The benefit of exercise testing in asymptomatic women is in determining their cardiovascular fitness.

Women need more fitness exercise independent of their weight, blood pressure, or lipid levels.

`9-9 ALCOHOL USE DISORDERS IN ELDERLY PEOPLE: Redefining An Age Old Problem In Old Age

Be vigilant for the role of alcohol when older people present with physical and psychiatric illness, cognitive impairment, and social problems. Use disorders may be more common in the elderly than you think .

Primary care clinicians should include sensitive questions about alcohol use in their systemic review of the patient history.

9-10 SELF ESTEEM AND HEALTH

There are two basic human needs—health and autonomy. Autonomy is closely linked with self esteem and the earning of respect. "Low levels of autonomy and low self esteem are likely to be related to worse health." Increasing pride in one's identity may have a more favorable effect on health behaviors and risks than focusing on how to change the risks themselves. There is a link between low self esteem and ill health. "All people have a basic need for autonomy and self esteem."

Primary care clinicians can enhance the self-esteem of patients with low esteem by listening carefully to their problems and showing respect and concern.

9-11 RISK OF ADENOCARCINOMA IN BARRETT'S ESOPHAGUS

"Patients with Barrett's oesophagus are at low risk of oesophageal adenocarcinoma. This risk is almost exclusively in patients with specialized intestinal metaplasia."

"Up to 8 years after diagnosis we found no increased risk of malignancy with time."

Surveillance of patients with BE at a risk of malignant transformation of 1% per year may be cost effective, but only in men over age 70. This questions the value of universal endoscopic screening for cancer in patients with BE.

Primary care clinicians in the USA refer patients with BE to gastroenterologists. They will usually advise periodic endoscopic screening .

9-12 ASSESSING THE SUCCESS OF SUCCESSFUL AGING

Clinicians must learn what their patients expect and value, and develop treatment plans that balance longevity with other facets of life. We should determine what social roles patients most value, what features of functioning are most important, and which strategies of treatment and prevention will optimize the chances of success *as the patient defines it.*

Successful aging is possible *despite disease and disability*. If our concept of successful aging includes dignity, autonomy, social engagement, and the absence of suffering, we will be better positioned to configure our system of care to address the needs of the elderly. Pursuing the myth of the *Fountain of Youth* is not the answer.

Success in aging is "what I say it is" and what I make it. I will not depend on my clinician or on the public health service to define it.

9-13 PATIENTS PUT THEIR RELATIONSHIP WITH THEIR DOCTORS AS SECOND ONLY TO THAT OF THEIR FAMILIES

A new international study given at the World Medical Association annual assembly reported that, although the doctor-patient relationship has become less paternalistic, it still holds a central and trusted place in society. The authors warn that, to keep this status, doctors will need to measure up to patients' higher expectations of care.

"The patient-physician relationship is part of the critical underpinnings of stable societies."

It is still a privilege to be a physician.

9-14 EFFECT OF ST JOHN'S WORT ON DRUG METABOLISM BY INDUCTION OF CYTOCHROME P450 3A4 ENZYME

Long-term dosing of St John's wort results in *induction* of the liver enzyme cytochrome P450 3A4. This hastens metabolism of many drugs and diminishes their plasma levels and clinical effectiveness. This leads to increased dosage requirements of the 50% of drugs metabolized by this liver enzyme.

St. John's wort can significantly alter the effectiveness and dosing of a wide range of medications.

Patients' use of herbal nostrums continues undiminished. "Natural" is considered harmless even by the most sophisticated patients. This is another good reason for primary care clinicians to insist that patients "brown bag" all medications they take at each office visit.

9-15 EFFECT OF MAGNETIC VS SHAM-MAGNETIC INSOLES ON PLANTAR HEEL PAIN: A RANDOMIZED CONTROLLED TRIAL

Magnetic insoles did not benefit any more than sham insoles. Many patients who use them will not be convinced despite this well-controlled study.

9-16 METHYLXANTHINES FOR EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

When given in conjunction with other standard treatments, methylxanthines did not confer statistically significant benefits for lung function, clinical outcomes, and symptoms in patients with exacerbations of COPD. They significantly increase nausea and vomiting.

9-17 PARATHYROID HORMONE PLUS ALENDRONATE—A Combination That Does Not Add Up

It would be plausible to assume that the effect of a bisphosphonate + parathyroid hormone would be additive, since their mechanisms of action differ. Unfortunately, this is not the case. Disappointing !

Apparently, alendronate impairs the anabolic activity of parathyroid hormone.

To Reduce Severity and Mortality, from Thromboembolic Stroke, Aim for INR of 2.5

9-1 EFFECT OF INTENSITY OF ORAL ANTICOAGULATION ON STROKE SEVERITY AND MORTALITY IN ATRIAL FIBRILLATION

AF-related cardioembolic strokes may be more severe than other types of ischemic stroke, and may carry higher mortality rates.

Oral anticoagulation is highly effective in preventing stroke in patients with AF. Studies have reported that full benefit of anticoagulation for prevention requires a target international normalized ratio (INR) of 2.0 or above.

This study asked. . . What is the effect of intensity of anticoagulation on *severity* of AF-related stroke and mortality?

Conclusion: Anticoagulation resulting in an INR of 2.0 to 3.0 greater reduced the *severity* of stroke and *risk of death* from stroke

STUDY

1. Followed over 13 500 patients (mean age 78) with non-valvular AF discovered on routine physician-visits.
2. Determined incidence of stroke on follow-up.
3. In those experiencing stroke, determined INR at admission, use of warfarin, aspirin, and no antithrombotic related to severity of stroke according to a stroke-scale, and 30-day mortality from stroke.
4. Follow-up = 30 days

RESULTS

1. 596 ischemic strokes occurred during follow-up . At the time of the stroke:

    188 (32%) occurred during warfarin therapy

    160 (27%) occurred during aspirin therapy;

    248 (42%) occurred in those who were receiving neither.

    (*Note that there were fewer strokes in patients on aspirin. The investigators did not assign individuals in the cohort to high, moderate, or low risk of stroke. Note that 4 of 10 were not receiving any prophylactic therapy RTJ.)*
2. Median INR of those taking warfarin was 1.7; 62% had levels less than 2.0

3. Intensity of anticoagulation associated with incidence of death or severe stroke (%):

INR 2.0 or greater	5
INR less than 2.0	15
Aspirin	13
On no antithrombotic	22

4. Proportion of those with severe or fatal stroke did not differ significantly between those with an admission INR 1.5 to 1.9 and those with an INR less than 1.5

5. Intensity of anticoagulation and 30-day mortality (%):

INR 2.0 and greater	6
INR less than 2.0	16
INR 1.5 to 1.9	18
INR less than 1.5	15
Aspirin	15
None	24

(*Low dose warfarin and aspirin conferred some protection*.)

6. Incidence of ischemic stroke and intracranial hemorrhage.

	Stroke (per 100 person –years)	Intracranial hemorrhage (per 100 person-years)
INR < 1.5	8	0.5
1.5-1.9	1.9	0.3
2.0-2.5	0.4	0.3
2.6 to 3.0	0.9	0.5
3.1 to 3.5	0.7	0.6
3.6 to 3.9	0.4	0.4
4.0-4.5	1.4	2.7
> 4.5	2.6	9.4

(Note the large jump in risk of hemorrhagic stroke at 4.0 and above. RTJ)

DISCUSSION

1. Incidence of ischemic stroke among patients with AF is greatly reduced when INR reaches 2.0 or above.
2. Strokes that occur among patients with adequate anticoagulation (2.0 to 3.0) are far less likely to result in severe disability or death. For those with an INR less than 2.0 who had an ischemic stroke, risk of death within 30 days was more than 3 times the risk among those with INR of 2.0 or greater.
3. Outcomes were equally poor among warfarin users with an INR of 1.5 to 1.9 at admission as those with an INR of less than 1.5. Outcomes were even worse for those who received no antithrombotic therapy.
4. Outcomes for those taking aspirin when they had a stroke were similar to that of patients with INR less than 2.0, but better than those taking no anticoagulation.

5. The American Heart Association suggests the use of lower INR target for certain patients with AF who are older than age 75. The data in this study indicate that this will likely increase disability and death.
6. In the study, there was little additional risk of intracranial hemorrhage until INR exceeded 3.9. These findings weigh against use of target INR less than 2.0.

CONCLUSION

"Our results provide further support for anticoagulation to achieve an INR of 2.0 or greater (aim for 2.5) in patients with nonvalvuar atrial fibrillation."

Among patients with nonvalvuar AF, the degree of anticoagulation at admission for stroke was associated with risk of disability and death. Anticoagulation that results in an INR of 2.0 or greater reduces frequency and severity of ischemic stroke and risk of death. This is evidence against INR targets below 2.0

Risk of hemorrhagic stroke did not increase until INR was over 3.9

NEJM September 11,2003; 349: 1019-26 Original investigation, first author Elaine M Hylek, Harvard Medical School, Boston Mass. www.nejm.org

An editorial in this issue of NEJM by Robert G Hart comments and expands:

Because the emboli of atrial origin are larger than average, the brain infarcts are more disabling and lethal. The average age of AF is about 75. Among the very elderly, AF is the single most important cause of ischemic stroke. Cardioversion (attempts at rhythm control) does not reduce risk of stroke. "When properly administered, adjusted dose warfarin virtually eliminates the excess risk of stroke associated with atrial fibrillation."

Aspirin reduces risk of stroke by about 20% compared with placebo. Optimum anticoagulation with warfarin is unequivocally superior to aspirin in preventing stroke in patients with AF.

Does it then follow that all patients with AF should receive lifelong anticoagulation? No. The risk of stroke varies by a factor of more than 20 among patients with AF. "Many patients with AF, including those under age 75, do not benefit sufficiently from anticoagulation to warrant its use instead of aspirin for primary prevention." About one in three patients with AF have a risk of stroke less than 2% per year if given aspirin. About one third have a high risk of stroke (over 4% a year). The rest are at moderate risk.

Adjusted-dose warfarin offers large benefits for high-risk patients. Aspirin is adequate for low-risk. For those with moderate risk, the patient's preference, individual risk of bleeding, and access to high-quality anticoagulation monitoring are crucial decision factors.

At present, there is no consensus about which criteria are best. But efficacious well-tolerated antithrombotic therapies to prevent stroke are underused in clinical practice.

Comment:

The study did not fully assess benefits in *prevention* of stroke. It made no attempt to stratify individual patients with AF for preventive measures into low, moderate, and high risk. It concerned only

those who experienced stroke (596 patients out of 13 559). It did not consider therapy with aspirin, low-dose warfarin or standard dose warfarin as *prevention* therapy of stroke. RTJ

9-2 ORAL XIMELAGATRAN FOR SECONDARY PROPHYLAXIS AFTER MYOCARDIAL INFARCTION

Platelet activation and thrombin generation are key mechanisms in the pathophysiology of acute coronary syndromes—ST elevation myocardial infarction **(MI),** non-ST elevation MI, and unstable angina.

Antithrombotic treatment is a cornerstone of treatment of acute coronary syndromes.

Soon after anticoagulation treatment stops, rebound ischemia and MI can occur. During subsequent months, morbidity and mortality remain high because of recurrent thrombotic events. Long-term aspirin is the mainstay of antiplatelet therapy. It reduces relative risk of MI, stroke, or vascular death by about 25%. Long term anticoagulation with warfarin further reduces cardiovascular events in patients with MI. Warfarin is associated with drug and food interactions and requires frequent monitoring, dose adjustment, and risk of bleeding, especially when combined with aspirin. New safer and more effective oral anticoagulants are being sought.

Ximelagatran is the first of a new class of oral direct-thrombin inhibitors under investigation. It is rapidly metabolized to its active form, melagatran, which is excreted mainly by the kidneys. It is stable over time. Its metabolism is unaffected by age, sex, body weight, or ethnic origin. It is not affected by the hepatic cytochrome P450 enzyme system, thus providing a low potential for drug-drug interactions. There are no relevant food or alcohol interactions. Ximelagatran's pharmacokinetics are unchanged and the pharmacodynamic properties show only minor additive effects when given with aspirin.

This study assessed effectiveness of ximelagatran *plus aspirin* on prevention of death, non-fatal MI, and severe recurrent ischemia after a recent MI.

Conclusion: Oral direct thrombin inhibition with ximelagatran added to aspirin was more effective than aspirin alone in preventing major cardiovascular events after a recent MI.

STUDY

1. Placebo-controlled, double blind dose-guided phase II trial assessed over 1800 patients who had a recent ST-elevation MI, or non-ST elevation MI.
2. Randomized within 14 days (mean = 7) of the MI to: 1) oral ximelagatran, twice daily, at doses of 24 mg, 36 mg, 48 mg, or 60 mg + aspirin 160 mg once daily; or 2) aspirin alone--160 mg once daily for 6 months.
3. Ximelagatran was begun within 6-12 hours after the end of heparin as a protection against rebound events, and as added secondary prevention.
4. Primary efficacy outcome = all-cause death, non-fatal MI, and severe recurrent ischemia.
5. Follow-up = 6 months

RESULTS

1. Oral ximelagatran combined with aspirin significantly reduced risk of the primary endpoint from 16%

to13%. [NNT (for 6 months to benefit one) = 33]

2. There was no indication of a dose response. (Ie, 24 mg just as effective as 60 mg.)
3. Major bleeding events overall: 1.8% vs 0.9% for aspirin alone. [NNT (to harm one patient over 6 months) = 100]
4. No other adverse outcomes related to the ximelagatran.

DISCUSSION

1. After an acute MI, oral ximelagatran combined with aspirin was more effective than aspirin alone in preventing a composite endpoint of death, non-fatal MI, and severe recurrent ischemia. Absolute difference was 3.6 % (NNT = 28) There was no dose response relation for efficacy—24 mg as effective as 60 mg.)
2. "The findings would support a hypothesis of a benefit . . . in prevention of other thromboembolic events such as stroke."
3. The benefits of ximelagatran seem to be of the same magnitude as clopidogrel in non-ST-elevation MI, or with warfarin after initial heparin treatment in all patients with MI. .
4. Elevated alanine transferase levels were dose related—much less pronounced rises occurred with the 24 mg dose.
5. In this trial there was no indication of difference in efficacy between the four doses of ximelagatran given in addition to aspirin. "These findings suggest that ximelagatran is effective at a wide range of doses with a low risk of bleeding."
6. Total bleeding rates (major and minor) were 1% higher with ximelagatran plus aspirin than with aspirin alone.
7. In the 24 mg dose group there was no difference in the rate of discontinuation from that seen with placebo.
8. Ximelagatran has been reported to be efficacious for prevention of venous thromboembolism and to be as effective as warfarin for stroke prevention in patients with atrial fibrillation.

CONCLUSION

Long term treatment with the oral direct thrombin inhibitor, ximelagatran, combined with aspirin , was more effective than aspirin alone in reducing frequency of major cardiovascular events in patients with a recent MI. [NNT(6 months to benefit one) = 28]

Lancet September 6, 2003; 362: 789-97 Original investigation, by the ESTEEM investigators, first author Lars Wallentin, University Hospital, Uppsala, Sweden. www.thelancet.com

Comment:

Study supported by Astra-Zeneca

An editorial in this issue of Lancet, first author Robert P Giugliano, comments:

Aspirin is effective in preventing death and severe ischemic complications after MI. However, patients still remain at high risk for subsequent events. Beyond aspirin, other options include warfarin, clopidogrel, and direct thrombin inhibitors. Warfarin is associated with increased risk of bleeding, particularly with combination therapy, and

there are hurdles in achieving safe anticoagulation (food and drug interactions, careful monitoring of dose, risk of fetal malformations).

Ximelagatran has undergone extensive assessment in patients with venous thromboembolism and atrial fibrillation. It has a rapid onset of action, achieves a peak level within 2 hours, and has a half-life of 4 hours. It is administered twice daily. This pharmacokinetic profile is predictable, and is not influenced by age, weight, sex, ethnicity or food. This permits fixed dosing without the need of monitoring and dose adjustments. (*Monitoring of liver and kidney function is required. RTJ*) Since it does not interact with the cytochrome P450 in the liver, there are fewer drug-drug interactions than with warfarin. Ximelagatran is primarily excreted by the kidney. Data on patients with kidney dysfunction are limited.

"It is good news that the more than half century wait of new and improved oral antithrombotics finally appears to be ending."

ACE inhibitor for Everyone with CAD?

9-3 EFFICACY OF PERINDOPRIL IN REDUCTION OF CARDIOVASCULAR EVENTS AMONG PATIENTS WITH STABLE CORONARY ARTERY DISEASE

Angiotensin-converting-enzyme inhibitors **(ACE-inhibitors)** reduce the rate of cardiovascular events among patients at high risk for such events.

In addition to lowering BP, ACE inhibitors possess direct cardiovascular protective effects through reduction in angiotensin II and increased availability of bradykinin. ACE-inhibitors may result in anti-atherosclerotic effects, reduce neointimal formation, improve endothelial function, and lead to plaque stabilization and fibrinolysis. This suggests that ACE inhibitors might be extended to *all* patients with established coronary disease.

This study assessed whether the ACE inhibitor perindopril (*Aceon*) would reduce cardiovascular risk in patients with *stable* coronary artery disease **(CAD)**—ie, those without apparent heart failure.

Conclusion: Among patients with stable CAD (without apparent heart failure), perindopril given in addition to other preventive drugs improved outcomes.

STUDY

1. Followed over 12 000 patients (mean age 60; almost all males) with established CAD. (History of myocardial infarction, angiographic evidence of CAD, coronary revascularization, or a positive stress test.) None had evidence of heart failure
2. Mean systolic BP = 137 mm Hg; 27% had hypertension
3. Randomized to: 1) perindopril 8 mg once daily, or 2) placebo.
4. Many were taking platelet inhibitors, beta-blockers, and lipid-lowering therapy.
5. Primary outcome = cardiovascular death, myocardial infarction, or cardiac arrest.
6. Follow-up—up to 5 years.

RESULTS

1. Outcome—5-years	Perindopril	Placebo	NNT

Primary endpoint	8%	10%	50

2. Secondary endpoints also benefited by perindopril treatment: 1% to 2% reductions occurred in heart failure requiring hospitalization, unstable angina, and MI (fatal and non-fatal).
3. "Perindopril was well tolerated." But 2.7% withdrew from perindopril (mainly for cough) vs 0.5% with placebo.

DISCUSSION

1. Perindopril was chosen because it is long-acting, has documented BP-lowering properties, and anti-ischemic and anti-atherogenic properties, as well as an effect of cardiovascular remodeling.
2. "We show a substantial benefit with perindopril in a broad population of patients with stable coronary artery disease and with no evidence of heart failure or notable hypertension. Cardiovascular death, myocardial infarction, cardiac arrest, acute coronary syndromes, and development of heart failure were all reduced."
3. Almost a third of patients in this study were younger than age 55.
4. Benefits of perindopril were evident when added to other secondary prevention drugs--platelet inhibitors, beta-blockers, and lipid-lowering agents.
5. Treatment effect was similar among patients with treated hypertension and those without hypertension.
6. The reduction in cardiovascular events was greater than may be expected for the 5/2 mm mean reduction in BP achieved by perindopril
7. Benefits began after one year of treatment. The gradual onset of effect and the progressive benefit over time is consistent with the anti-atherosclerotic and anti-hypertensive properties of ACE inhibition.
8. An estimated 50 patients need to be treated with perindopril for a period of 4 years to prevent one major cardiovascular event.

CONCLUSION

Among patients with stable coronary heart disease without apparent heart failure, perindopril can significantly improve outcome. "Treatment with perindopril, in addition to other preventive medications, should be considered in all patients with coronary heart disease." **1**

Lancet September 6, 2003; 362: 782-88 Original investigation by the European Trial On Reduction of Cardiac Events with Perindopril in Stable Coronary Artery Disease (EUROPA) investigators. Correspondence to K M Fox, Royal Brompton Hospital, London, UK www.thelancet.com

An editorial in this issue of Lancet (pp755-57) by Harvey D White, Green Lane Hospital, Auckland, New Zealand comments;

"Should all patients with coronary disease receive angiotensin-converting-enzyme inhibitors?"

ACE inhibitors have been shown to have the broadest impact of any drugs in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, post

myocardial infarction left ventricular dysfunction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks. The preceding trial shows that ACE also benefits patients with *stable* coronary artery disease who presumably had normal left ventricular function.

The renin-angiotensin system may influence the etiology of plaque fissuring and rupture. This effect could account for the benefits of ACE inhibitors because agents with tissue effects may counter the deleterious effects of angiotensin II, improve endothelial function, and hinder development of atherosclerosis and thrombosis.

A previous study of the effects of the ACE inhibitor ramipril (NEJM 2000; 342: 145-53) concerned over 9000 high risk patients with vascular disease or diabetes and other risk factors. Ramipril reduced the combined rate of cardiovascular death, myocardial infarction, and stroke from 18% to 14%.

Comment:

1 As noted above**,** investigators, journal editors, and peer reviewers often conclude that the drugs they study are associated with "significant" benefits. They usually mean *statistically* significant benefits, not necessarily *clinically* significant benefits. I believe the conclusion that treatment with perindopril, in addition to other preventive medications, should be considered in all patients with coronary heart disease is an overstatement. No doubt, however, that reduction of angiotensin is basic treatment of cardiovascular disease.

The patients should be informed that the $2000 will gain him a one in 50 chance of avoiding a primary event in 4 years—at the risk of intolerance to the drug of at least one in 50.

The decision to use perindopril must be negotiated with each individual patient. Perhaps use of a generic ACE inhibitor would be more acceptable. Generic enalapril (*Vasotec 10 mg*) costs 31 cents each. RTJ

Study supported by Servier, France.

==========

9-4 LIFETIME RISK OF CORONARY HEART DISEASE BY CHOLESTEROL LEVELS AT SELECTED AGES.

How do cholesterol levels at different ages modify the remaining lifetime absolute risk of coronary heart disease (CHD)? The Framingham investigators previously developed multivariate risk equations for estimating 10-year absolute risk of developing CHD. However, reliance on estimates of relatively short-term absolute risk to make treatment decisions is problematic. Long-term risk assessment is particularly relevant for younger patients with risk factors for CHD in whom exclusive attention to short-term risk may discourage initiation of, or adherence to, treatment.

Lifetime risk estimates account for the risk of the disease of interest and the competing risk of death from other causes. The estimates provide a simple conceptual basis for assessing the absolute risk of developing CHD during the remaining lifespan. They answer the question … What is the chance of developing CHD before dying of something else?

The Framingham Heart Study followed a defined cohort long-term, and carefully documented risk factors and events. This provided a unique opportunity to assess how cholesterol levels modify remaining lifetime risk for CHD.

Conclusion: Lifetime risk of CHD increases sharply with higher total cholesterol levels for men and women of all ages. Screening should be universal in order to institute lipid control.

STUDY

1. Included all Framingham participants examined from 1971 through 1996 who did not have CHD and were not receiving lipid-lowering therapy.
2. Participants were stratified by total cholesterol levels at index ages of 40, 50, 60, 70, and 80 years.
3. Calculated lifetime risk of CHD with death free of CHD as a competing event over the next 25 years.

RESULTS

1. During follow-up, among over 3200 men and over 4000 women, 1120 died of CHD and 1365 died free of CHD.
2. At each index age, lifetime risk of CHD (fatal and non-fatal) increased with higher cholesterol levels, and the time to event decreased. Lifetime risk of CHD (%):

Index age	Total cholesterol (men)			Total cholesterol (women)		
	< 200	200-239	>239	< 200	200-239	> 239
40*	31	43	57	15	26	33
50**	40	42	63	19	30	39
60#	34	41	51	20	24	36
70#	27	36	42	14	20	29
80#	17	23	34	17	17	21

(* lifetime risk through age 80 ** lifetime risk through age 90 # lifetime risk through age 94)

3. These long-term risks can be compared with short-term risks. For young participants, short-term risk of CHD is exceedingly low, even with elevated cholesterol levels, whereas life-time risks are high, especially for those with elevated cholesterol. At age 40, the 10-year risk of CHD for men:

Cholesterol < 200	3%
Cholesterol 200 to 239	5%
Cholesterol > 239	12%

DISCUSSION

1. In men and women across the age spectrum who were free of CHD at baseline, total cholesterol levels were extremely effective at stratifying the remaining life-time risk of CHD.
2. There was a 1.5- to 2-fold higher absolute remaining lifetime risk of CHD for men and women with elevated, compared with desirable cholesterol levels. (Eg, at age 40, the lifetime risk of CHD through age 80 was 31% for men with desirable levels, and 57% for men with elevated levels.
3. Even at age 80, elevated total cholesterol levels conferred substantially higher remaining lifetime risk.
4. The remaining lifetime risk diminishes with advancing age, likely reflecting both depletion of susceptible individuals and increasing risk of death from other causes.
5. It is clear that cholesterol levels do not account for all the lifetime risk of CHD. Other risk factors contribute—smoking, hypertension, and diabetes.
6. The present study has the advantage of accounting for non-fatal coronary events, which are associated

with substantial morbidity.

7. The current national guidelines recommend that all adults 20 years and older have a complete lipoprotein profile at least once every 5 years. (Determination of LDL-c and HDL-c and their ratios may sharpen the predictive value.)
8. "Our data highlight the utility of total cholesterol measurement in young adults (both men and women) for stratifying remaining lifetime risk of CHD and for identifying remaining lifetime risk."
9. In younger individuals with elevated cholesterol and low short-term risk, informing them of their high lifetime risk might be more useful in motivating lifestyle modifications.
10. Hypercholesterolemic participants have a markedly shorter time-to-event to reach a threshold of 20% for the cumulative lifetime risk of CHD.
11. In older individuals (70s and 80s) with higher cholesterol levels the increased risk of CHD indicates the near-term importance of interventions to control lipids.

CONCLUSION

Lifetime risk of CHD increases as total cholesterol levels rise from under 200 to over 240 for person of all ages. This supports the important role of cholesterol screening at all ages.

Archives Int Med September 8, 2003; 163: 1966-72 Original investigation, first author Donald M Lloyd-Jones, National Heart, Lung and Blood Institute, Framingham Heart Study, Framingham Mass. www.archinternmed.com

Comment:

This article is of considerable clinical importance even though it provided no outcomes from lifestyle or drug interventions. Patients, old and young, now have a reasonable prediction of lifetime risk according to total cholesterol levels. (And cholesterol subfractions.) Old, and young should be screened periodically. The data may convince some younger persons to intervene to reduce their lifetime risk. RTJ

The Framingham Coronary Disease Risk Prediction Score (10-year) is calculated from age, total cholesterol, HDL cholesterol, BP, diabetes, and smoking. It is accessible on the Internet along with the latest guidelines for lipid control. www.nhlbi.nih.gov/guidelines/cholesterol/atglance.pdf

---

Is Common, Underdiagnosed, Impairing, And Treatable

9-5 SOCIAL ANXIETY DISORDER

The hallmark of social anxiety disorder **(SAD)** is extreme and persistent fear of embarrassment and humiliation. People with SAD (also known as social phobia) often avoid participating in social and public activities such as public speaking, social gatherings, and meetings. The intense symptoms of SAD interfere with functioning and cause marked distress.

It differs from other phobic disorders by a characteristic age of onset (mid-teens) and greater ratio of men to women. It is the third most prevalent psychiatric disorder in the U.S. Lifetime prevalence in the community may be as high as 12%.

It often remains undiagnosed. The reticence and shame that are intrinsic to the disorder inhibit help-seeking. Patients usually come for treatment only after years of suffering. They may present initially with a complication -- major depression or alcohol abuse. There may be substantial genetic and environmental contributions to the disorder.

Clinicians can encourage patients to discuss their symptoms by including a brief query into social anxiety or social avoidance in a review of systems assessment. In feared situations, patients with SAD experience self-consciousness, embarrassment, and difficulty speaking, Symptoms of autonomic arousal occur: blushing, sweating, trembling, and palpitations. Thoughts often dwell on inferiority to others, desire to flee, and anticipatory negative evaluation by others. Weeks of anxiety may precede a social event.

Patients with a milder form of SAD may be comfortable in informal social situations, but experience distressing or impairing anxiety attacks during public speaking or performance. SAD can be differentiated from panic disorder by its consistent relation to social issues.

The best established treatment for SAD is cognitive behavior therapy and serotonin reuptake inhibitors. Paroxitine (*Paxil*) and sertraline (*Zoloft*) have been effective.

BMJ September 6, 2003; 327: 515-16 Editorial by Franklin R Schneier, New York State Psychiatric Institute, New York, NY. www.bmj.com/cgi/content/full/327/7414/515

Comment:

SAD is panic under limited circumstances. There is another social anxiety which is even more common. Many individuals fear speaking and performing in front of audiences. Musicians may develop tremors, making playing difficult. For some reason, the article did not mention beta-blockers. They can be transiently helpful in mild cases of performance anxiety (public speaking, instrument playing, singing, teaching).

The same acronym (SAD) has been applied to seasonal affective disorder, depression associated with long, dark winters. RTJ

***Angiotensin II Blocker Reduced Cardiovascular Deaths And Hospital Admission For HF*.**

9-6 EFFECTS OF CANDESARTAN ON MORTALITY AND MORBIDITY IN PATIENTS WITH CHRONIC HEART FAILURE (The CHARM-overall Programme)

Heart failure **(HF)** is the most common reason for hospital admission in patients older than 65 years.

Patients with chronic HF are at high risk of cardiovascular death and recurrent hospital admissions. In patients with HF and reduced left-ventricular ejection fraction (LVEF) , angiotensin-converting-enzyme inhibitors **(ACE)** show life-saving and symptomatic benefits. But, about 35% to 50% of patients with signs and symptoms of CHF do not have substantially reduced LEVF.

Angiotensin II blockers such as candesartan (*Atacand*) inhibit the effects of the renin-angiotensin-aldosterone system at the cellular level. They may improve clinical outcomes when added to ACE inhibitors in patients with HF.

The study asked. . . Would the use of this angiotensin II receptor blocker **(AIIRB)** reduce mortality and morbidity in patients with HF when *added* to other standard drug therapy, including ACE inhibitors.

Conclusion: In patients with chronic HF, adding candesartan to other therapy was associated with reduced cardiovascular deaths and hospital admissions for HF.

STUDY

1. Randomized, double-blind, controlled trial of over 7600 patients with HF (45% with NYHA class II, 52% with class III, 3% class IV; mean age = 66), compared candesartan with placebo.
2. It involved 3 distinct populations of patients with HF:
   Patients with left ventricular ejection fraction **(LVEF)** less than 40% who were *not* taking ACE inhibitors.
   Patients with LVEF less than 40% who were taking ACE inhibitors.
   Patients with LVEF higher than 40%.
3. Randomized to: 1) candesartan titrated up to 32 mg once daily, or 2) placebo. Other drugs were continued.
4. Primary outcome = all-cause mortality, cardiovascular death and hospital admissions for HF.
5. Median follow-up = 38 months.

RESULTS

1. Outcomes (3 groups combined)	Candesartan	Placebo	NNT 3 years to benefit one patient
All-cause deaths	23%	25%	50
Cardiovascular deaths	18%	20%	50
Hospital admissions for HF	20%	24%	25

2. More patients discontinued candesartan (21%) than placebo (17%) because of concerns about renal function, hypotension, and hyperkalemia. [NNT(harm to one patient over 3 years) = 25
3. Benefits were strongly affected by left ventricular systolic function. In the group with LVEF over 40%, candesartan did *not* improve survival. (Ie, no definitive benefit in patients with "normal" ejection fraction--those with "diastolic" HF)
4. In the two groups with low LVEF there was a clear prolongation of survival and a 16% lower rate of cardiovascular death. This was complemented by a significant reduction in hospital admission for HF.
5. Beneficial effects were similar irrespective of other drug use at baseline—ACE, beta-blockers, spirinolactone, diuretic, digitalis, aspirin, and/or statins.
6. There was a reduction in the number of candesartan patients developing diabetes over the trial duration (6% vs 7.4% in the placebo group).

DISCUSSION

1. Treatment of a broad spectrum of patients with symptomatic HF with candesartan was associated with a reduction in deaths (albeit of borderline statistical significance), notably because of a significant reduction in cardiovascular deaths.
2. Blockade of angiotensin II at the cell-receptor level, given in addition to the partial inhibition of angiotensin II

production by ACE inhibitors, can result in more complete inhibition of the adverse cardiovascular effects of angiotensin II. It may leave unopposed potentially *desirable* effects of angiotensin II on other receptors. AIIRBs effectively reduce important clinical events in hypertensive patients with diabetes and neuropathy, hypertensive patients with EKG evidence of left ventricular hypertrophy, elderly patients with hypertension, and those with HF and depressed ejection fraction.

3 The reduction in cardiovascular death with candesartan was similar in 2 groups: 1) those taking ACE inhibitors and those not taking ACE inhibitors. Benefits from candesartan were also present irrespective of beta-blocker use. The added efficacy on top of beta blockers is particularly noteworthy.

4 Patients who are intolerant to ACE inhibitors should not be denied the benefits of angiotensin-receptor blockade.

5. Patients who have symptomatic heart failure will derive important clinical benefits from candesartan."

CONCLUSION

In patients with chronic heart failure associated with a low ejection fraction, candesartan significantly[1] reduced cardiovascular deaths and hospital admissions for heart failure. The benefit was consistent irrespective of concomitant use of other effective drugs, including ACE inhibitors.

Lancet September , 2003; 362: 759-66 Original investigation by The Candesartan in Heart failure Assessment of Reduction in Mortality and Morbidity (CHARM) program, first author Marc A Pfeffer, Brigham and Women's Hospital, Boston, Mass. www.thelancet.com

Two editorials by Harvey D White, Green Lane Hospital, Auckland, New Zealand in this issue of Lancet (pp 754-55; pp 755-56) comment:

The CHARM is the largest trial program ever undertaken in heart failure patients.

"ACE inhibitors have been shown to have the broadest impact of any drug in cardiovascular medicine, reducing the risk of death, myocardial infarction, stroke, diabetes, and renal impairment. They benefit patients with heart failure, left ventricular dysfunction post myocardial infarction, peripheral vascular disease, diabetes, stroke, and transient ischemic attacks. "

There were adverse effects from candesartan. Hyperkalemia and doubling of creatinine concentrations occurred and require monitoring, particularly when patients were also receiving ACE inhibitors. These adverse effects are likely to be more common in clinical practice.

AIIRBs should be prescribed in addition to ACE inhibitors, beta-blockers, and/or spirinolactone in patients with HF and an ejection fraction less than 40%, and as an alternative to ACE inhibitors in patients with ACE inhibitor intolerance.

Comment:

1 Investigators like to mention that their results are "statistically" significant. But are they "clinically" significant? *Atacand* (32 mg daily) now costs $2 each tablet. To some patients, this may be a minor expense; to some prohibitive. Patients should understand that it will benefit only one in 25 to 50 over 3 years; and harm one in 25. RTJ

==========

Most Patients Have Comorbidities That Need To Be Addressed

9-7 POLYPHARMACY AND COMORBIDITY IN HEART FAILURE

The care of patients with heart failure **(HF)** is becoming more complex. Guidelines now include agents that prolong life, alleviate symptoms, and reduce hospital admissions.

Simultaneously, the treatment of underlying causative factors has evolved (hypertension, coronary artery disease, dyslipidemia, diabetes). The burden of HF falls disproportionately on elderly people who are simultaneously afflicted with other conditions (chronic obstructive pulmonary disease, atrial fibrillation, prior stroke). This increases the number of drugs considered necessary for many patients with HF. Primary care clinicians face the challenge of managing not a single condition, but multiple conditions requiring multiple medications.

Little evidence is available to guide polypharmacy in patients with HF and other common conditions. The strongest evidence supporting individual drugs derives primarily from randomized trials which typically exclude older patients and patients with multiple comorbidities. Some trials use run in periods to assess tolerance—an approach that may constrain applicability of the results.

Clinicians need to have systems in place to review medication lists with a goal of eliminating medications that are not known to provide clear benefits. Specifically, in patients with HF, many antiarrhythmics, non-dihydropyridine calcium blockers (eg, diltiazem; verapamil), metformin, thiazolidinediones, and NSAIDs may be contraindicated. In patients with renal insufficiency, drug dosages need to be adjusted for the estimated glomerular filtration rate.

"The most urgent issues include the ideal dosing of medications, the appropriate use of potentially life saving drugs in patients with multiple competing comorbidities, and the treatment of coexisting illnesses in the context of heart failure."

BMJ September 6, 2003; 327: 513-14 Editorial, first author Frederick A Masoudi, Denver Health Medical Center, Denver CO. www.bmj.com/cgi/content/full/327/7414/513

Comment:

One of the rewarding functions of the primary care clinicians is to oversee, regulate, and eliminate some of the medications their consulting patients bring with them. Multiple doctors = multiple drugs.

Too many patients, especially the elderly are taking too many drugs. There is no way to determine adverse interactions between multiple drugs—sometimes ten or more—patients are taking. Cost is also an important factor. Is the patient getting his dollar's worth in additional benefit when the 9^{th} or 10^{th} drug is added? RTJ

9-8 ***Fitness, Not ST Segment Depression, Determines Prognosis***

ABILITY OF EXERCISE TESTING TO PREDICT CARDIOVASCULAR AND ALL-CAUSE DEATH IN ASYMPTOMATIC WOMEN: A 20-YEAR FOLLOW-UP OF THE LIPID RESEARCH CLINICS PREVALENCE STUDY

Two thirds of sudden deaths in women occur without previous symptoms. While ischemic ST changes have proven helpful in identifying men at risk for cardiovascular disease and increased mortality, they have proven unreliable in asymptomatic women. The current study attempted to determine if any exercise testing variables were of benefit in identifying women at risk.

Conclusion: Impaired exercise performance predicted increased cardiovascular mortality. ST depression did not.

STUDY

1. Entered over 2900 asymptomatic women age 30-80 (Mean = 42). None had known cardiovascular disease. Exercised all using Bruce protocol. Test terminated at 90% predicted maximum heart rate; or if hypotension, EKG changes of ischemia, or significant arrhythmia occurred.
2. At baseline, determined exercise test variables related to ischemia, fitness, and autonomic function:
    A. ST segment depression defined as >1.0 mm depression at 0.08 seconds after J point.
    B. Arrhythmia defined as multifocal pvcs, >10% pvcs, or ventricular tachycardia.
    C. Heart rate recovery **(HRR)** determined by subtracting pulse rate after 2 minutes rest from maximal heart rate during exercise.
    D. Exercise capacity—not able to achieve target rate.
3. Patients were followed annually for 20 years.
4. Main outcome = cardiovascular and all-cause deaths.

RESULTS

1. Fourteen percent of the cohort died during follow-up of an average 20 years; 34% of all deaths were cardiovascular.
2. Low exercise capacity, not achieving target heart rate on exercise, and low heart rate recovery were all independently associated with increased cardiovascular and all-cause mortality. Women who exceeded average exercise capacity (7.5 METS) and had a HRR of 55/minute or more had fewer cardiovascular deaths and all-cause deaths.
3. There was a graded increase in mortality for decreasing quintiles of exercise capacity and HRR.
4. There was no increased cardiovascular death risk associated with exercise-induced ST segment depression.
5. Multivariable-adjusted risk of deaths according to exercise test variables:

Variable	CV deaths (Hazard ratio)
Exercise capacity < median (7.5 METS)	1.9
Heart rate recovery < median (55 beats per minute)	2.2
Target heart rate not achieved	1.5
Ventricular arrhythmia	1.7
ST depression > 1.0 mm	0.88

6. Women below the median for both exercise capacity and HRR had a 3.5-fold increased risk of cardiovascular death compared with those above the median for both.

DISCUSSION

1. Exercise capacity and heart rate responses were strong, graded, and independent predictors of cardiovascular and all-cause mortality.
2. ST segment depression, while predictive in men, had no value in women.
3. Women need more fitness exercise independent of weight, blood pressure, or lipid levels.

CONCLUSION:

Fitness determined by exercise testing predicted future cardiovascular and all-cause mortality risk in asymptomatic younger women. ST segment depression was not predictive.

JAMA September 24, 2003; 290: 1600-1607 First author Samia Mora, John Hopkins Bloomberg School of Public Health, Baltimore, MD. www.jama.com

Article abstracted by Coleman D. Carter, M.D.

I think practitioners have become so focused on ST segments that we have assumed that exercise testing in women was worthless. This study suggests otherwise. Exercise and exercise tolerance continue to show up as independent risks factors for survival. CDC

Comment:

The main message is *not* using exercise testing as a predictive value, but to encourage unfit younger women to get in shape and stay in shape. RTJ

==========

No More Than One Drink A Day.

9-9 ALCOHOL USE DISORDERS IN ELDERLY PEOPLE: Redefining An Age Old Problem In Old Age

Alcohol use disorders **(AUDs)** in elderly people are common and associated with considerable morbidity. The absolute number of old people with AUDs is increasing. A "silent epidemic" may be evolving.

We need to improve appropriate screening and treatment methods and services. AUDs in elderly people are often under-detected and misdiagnosed. Most instruments and diagnostic criteria are geared towards younger people.

This systematic review considers aspects of the problem.

How common is the problem?

Although prevalence of AUDs in the elderly is generally accepted to be lower than in younger people, the rates may be underestimated because of under-detection and misdiagnosis. Rates of AUDs vary depending on the restrictiveness of diagnostic criteria used. AUD among elderly in the USA is estimated at 2% to 4%. When looser criteria, such as "excessive alcohol consumption" is used, up to 17% of elderly men and 7% of elderly women are so classified.

In general, the prevalence is greater for elderly patients who are hospitalized than those in the community.

Being male, socially isolated, single, and separated or divorced increase prevalence.

Reasons for underdetection and misdiagnosis:

Reasons are varied. Fewer than half of these patients have documentation of alcohol misuse in their medical records. The elderly may be reluctant to disclose their excessive alcohol intake. Healthcare workers have a lower degree of suspicion when assessing older people. Healthcare workers may perceive alcohol use in the elderly as being understandable in the context of poor health and changing life circumstances. This leads to therapeutic nihilism.

Presentation of the elderly with AUDs may be atypical (falls, concussion, depression) or masked by co-morbid physical of psychiatric illness. This makes detection difficult.

"Sensible" limits for weekly intake (21 units in men and 14 in women) may not apply to older people because of age-related changes in metabolism and increasing sensitivity to the effects of alcohol. The National Institute of Alcohol Abuse and Alcoholism recommends that persons over age 65 consume no more than one drink a day. Markers for AUDs (eg, CAGE and other questionnaires, mean corpuscular volume, gamma-glutamyl transferase) may not apply to the elderly.

Elderly people may be less likely than young people to encounter the social, legal, and occupational complications associated with AUDs, and more likely to encounter adverse physical health consequences.

An accurate assessment of *lifetime* alcohol consumption is essential when assessing AUDs in the elderly.

Effects of alcohol use in elderly people:

AUDs in the elderly are associated with widespread impairments in physical, psychological, social, and cognitive health. Equivalent amounts of alcohol produce higher blood alcohol concentrations in the elderly. Serious medical disorders among the elderly who misuse alcohol are much more common than in the general population of a similar age. Associations with having ever been a heavy drinker are long-lasting. Those affected have more major illnesses, poorer self-perceived health status, more visits to the doctor, more depressive symptoms, less satisfaction with life, and smaller social networks.

Potential health benefits:

In recent years, prominence has been given to the potential health benefits of alcohol. It has been suggested that light consumption is associated with reductions in risk of coronary heart disease, stroke, and dementia. However, the medical profiles and social characteristics of those who drink modestly may differ from those of non-drinkers or heavy drinkers.

Treatment of AUDs in elderly people:

The elderly have been shown to be at least as likely to benefit from treatment as the young. Understanding this may combat the nihilism associated with AUDs in older people.

If the patient requires tertiary treatment, detoxification should be accomplished in the hospital with correction of electrolyte imbalances and thiamine administration to prevent Wernicke's and Korsakoff's syndromes. Benzodiazepine-assisted withdrawal should be undertaken with care. The opioid-antagonist naltrexone (*generic*) has been shown to help prevent relapse.

The sizable proportion of elderly people who develop AUDs with late onset should be addressed at the primary prevention level. AUDs may rise *de novo* in elderly people in the context of bereavement, changing

roles, or illness. Modified screening instruments and diagnostic criteria for older people should focus on the more subtle yet damaging effects of alcohol on different aspects of health, with due account taken of increased co-morbidity while de-emphasizing some of the social, legal and occupational aspects that may be of more relevance to younger people.

Secondary prevention strategies should focus on elderly people whose drinking pattern, while not fulfilling criteria for alcohol misuse or dependence, may be putting their physical or psychological health at risk. For example, a moderate intake of alcohol may put an older person who is taking warfarin at risk for bleeding. (They may not have been informed that alcohol does interfere with their anticoagulation,)

Health care workers in all settings should be vigilant for the role of alcohol in the presentation of older people with physical and psychiatric illness, cognitive impairment, and social problems.

BMJ September 20, 2003; 327: 664-67 "Clinical Review", commentary, first author Henry O'Connell, St James's Hospital, Dublin Ireland. www.bmj.com/cgi/content/full/327/7416/664

Comment:

I believe the primary care clinician, once trust is established, can determine if AUD is a problem. For many patients merely uncovering the problem and getting the patient to admit it will lead to considerable lessening of alcohol intake.

Family members may give evidence of abuse by their elderly relatives. Establish trust with the family as well as the patient. RTJ

==========

Appropriate Reward For Efforts Expended And Control Over Life Circumstances Are Crucial

9-10 SELF ESTEEM AND HEALTH

Autonomy, self esteem, and health are linked together.

Society is riddled with inequality: of natural endowment and talent, of opportunities and life chances, and of achievement. These inequalities will be accompanied by inequality of respect. This, in turn will be accompanied by inequality of self esteem. Do inequalities of self esteem matter? If they do, is there anything to be done, given that there will always be individual differences in earned respect?

The answer to both questions is probably yes—they do matter, and something can be done.

Some authorities have stated that there are two basic human needs—health and autonomy. Autonomy is closely linked with self esteem and the earning of respect. "Low levels of autonomy and low self esteem are likely to be related to worse health." Increasing pride in one's identity may have a more favorable effect on health behavior and risks than focusing on how to change the risks themselves. There is a link between low self esteem and ill health. "All people have a basic need for autonomy and self esteem."

One study reported a close relation between the degree of income inequality and the rates of homicide. Accounts of life in the inner city emphasize the salience of respect and self esteem. "No small amount of mayhem is committed every year in the name of injured pride." Putting this together with income inequality, the hypothesis is that unequal distribution of resources leads to increased competition for status among young men who have

little to lose other than their self esteem and the respect of others. The results are violent confrontation and homicide. Where inequality is high, people at the bottom of the scale may express their response to threats to their self esteem in violent ways.

Several studies have shown links to increased coronary risk with low control in the work place and imbalance between efforts and rewards. “Appropriate reward for efforts expended and control over life circumstances are crucial for the enhancement of self esteem.” Threats lead to health-damaging behaviors and to activation of biological stress mechanisms that increase risk of diseases such as coronary artery disease. These threats are unequally distributed in society and hence may contribute to inequalities in health. Encouraging people off welfare and into work sounds like a step in the right direction. The quality of the job matters. Demeaning experiences in low paying jobs contradict the idea that any job is better than none.

What can be done? “To criticize inequality and desire equality is not to cherish the romantic illusion that men are equal in character and intelligence. It is to hold that, while their natural endowments differ profoundly, it is the mark of a civilized society to aim at eliminating such inequalities as have their source, not in individual differences, but in social organization.

BMJ September 13, 2003; 327:574-75 www.bmj.com/cgi/content/full/327/7415/574

Comment

Physicians, by treating the most humble persons with kindness, attention and respect, can do much to increase their feelings of self-esteem and self-worth. RTJ

==========

Not As High As Previously Reported

9-11 RISK OF ADENOCARCINOMA IN BARRETT’S ESOPHAGUS

Barrett’s esophagus is a metaplasia of the normal squamous epithelium to columnar epithelium. Goblet cells may be present. It is associated with chronic gastroesophageal reflux disease.

“Endoscopic surveillance of Barrett’s esophagus **(BE)** is now routine.” Cost-effectiveness depends on the risk of adenocarcinoma. The magnitude of the risk is not clear. Most previous studies were small and inconclusive.

This study investigated the risk of esophageal malignancy in a large cohort of unselected patients with BE in Northern Ireland, where all incident cancers are routinely identified.

Conclusion: Patients with BE are at *low* risk for esophageal carcinoma.

STUDY

1. Examined the pathology reports related to all esophageal biopsies in Northern Ireland between 1993 and 1999.
2. Included every adult identified as having columnar epithelium, excluding those taken from the esophageal-gastric junction.
3. Identified BE as the presence of columnar metaplasia in the esophagus irrespective of whether Barrett’s mucosa

was reported. Further subdivided biopsies if the pathologist specifically stated that specialized intestinal metaplasia, or goblet cells, were definitely present or absent.

4. Identified patients in the cohort and followed them up for death and esophageal malignancy.

RESULTS

1. Between 1993 and 1999, over 15 000 esophageal biopsies from almost 3000 patients met criteria for BE. Mean follow-up = 3.7 years.
2. 29 esophageal malignancies were discovered in over 11 000 person years of follow up. Esophageal malignancy rate was 0.26% a year overall and 0.4% a year for patients with specialized intestinal metaplasia. Only in men over age 70 with specialized intestinal metaplasia was the incidence greater than 1% per year.

DISCUSSION

1. "Patients with Barrett's oesophagus are at low risk of oesophageal adenocarcinoma. This risk is almost exclusively in patients with specialized intestinal metaplasia."
2. Surveillance of patients with BE at a risk of malignant transformation of 1% per year may be cost effective, but only in men over age 70.
3. "Up to 8 years after diagnosis we found no increased risk of malignancy with time."

CONCLUSION

Patients with BE are at low risk for esophageal adenocarcinoma. The risk is almost exclusively in patients with specialized intestinal metaplasia. Surveillance for BE in patients at risk of 1% per year may be cost effective. This risk occurs only in men age 70 or more.

BMJ September 6, 2003; 327: 534-35 Original investigation, first author Liam Murray, Queen's University of Belfast **www.bmj.com.cgi/content/full/327/7414/534**

Sickness And Dependency Do Not Necessarily Constitute A "Failure" In Aging.

9-12 ASSESSING THE SUCCESS OF SUCCESSFUL AGING

Despite the certainty of death, we increasingly (and exclusively) apply the yardstick of "success" to life's final chapter. No one speaks of "successful infancy", or "successful adolescence". There is something almost oxymoronic about the notion of successful aging. Perhaps it is this very contradictory quantity that attracts us. It allows us to envision an old age that is positive, productive, and hopeful.

What exactly do we mean by successful aging? How does this concept advance the challenging work of improving the lives of older people? What does the concept mean for clinical practice?

What Is Successful Aging?

The author has described development of two distinct schools in the history of gerontology:

1) The *psychosocial* school primarily defines successful aging as a mental state (for example,

acceptance of death, life satisfaction).

2) The *biomedical* school defines it as the avoidance of disease and disability.

"We badly need a synthesis of these two approaches."

We can list several areas of general agreement:

1) Successful aging means something beyond health and longevity. It is rooted in a broader definition of "the good life" in late-life. It refers to the capacity to function across many domains, including the cognitive, social, and emotional.

2) Successful aging is in large part what older adults value in the quality of their life and death.

3) Successful aging implies aging that is better than "usual aging", which many envision as lock-step declines in capacity and health. Herein lies both the promise and the danger of the concept. The promise comes from envisioning exceptional functioning as possible; the danger is concluding that sickness and dependency constitute a "failure" in aging.

Successful aging prompts the question of what we mean as "unsuccessful" aging. "To the extent that we conceptualize successful aging . . .as only disease-free aging, our concept (and our policies) will be impoverished."

How Can Successful Aging Be Useful?

"Successful aging is an organizing principal that serves as a source of conscience for medicine, public health, and gerontology. " Interventions in health behavior and health services have a goal of increasing the chances that older persons can age successfully. This leads to three unsettling conclusions:

1) Many interventions aimed at maximizing successful aging have not worked.

2) Interventions that work have not been implemented.

3) Existing health care systems in the USA are not well designed for the purpose of successful aging.

If taken seriously, successful aging requires substantial reorganization of health care systems, new and different outcome measures, and reconfigured funding strategies and priorities. We need to know considerably more about what older people value and how they define successful aging. "We have a long way to go."

Successful Aging And Clinical Practice

Clinicians must learn what their patients expect and value, and develop treatment plans that balance longevity with other facets of life. We should determine what social roles patients most value, what features of functioning are most important, and which strategies of treatment and prevention will optimize the chances of success *as the patient defines it.* Successful aging is possible despite disease and disability. If our concept of successful aging includes dignity, autonomy, social engagement, and the absence of suffering, we will be better positioned to configure our system of care to address the needs of the elderly. Pursuing the myth of the *Fountain of Youth* is not the answer.

Annals Int Med September 2, 2003: 139: 383-83 Editorial by Thomas A Glass, Johns Hopkins University School of Hygiene and Public Health, Baltimore MD. www.annals.org

Comment:

Success in aging is "what I say it is" and what I make it. I will not depend on my clinician or on the public health service to define it. RTJ

Physicians Still Hold A Central And Trusted Place In Society

9-13 PATIENTS PUT THEIR RELATIONSHIP WITH THEIR DOCTORS AS SECOND ONLY TO THAT OF THEIR FAMILIES

A new international study given at the World Medical Association annual assembly reported that, although the doctor-patient relationship has become less paternalistic, it still holds a central and trusted place in society. The authors warn that, to keep this status, doctors will need to measure up to patients' higher expectations of care.

The study described the perceptions of over 3500 patients in 6 countries. Patients felt more confident and empowered than they did 10 years ago in dealing with the medical profession.

Only a minority of patients (17% in the USA) defined the patient-doctor relationship as authoritarian or paternalistic. And in all countries the relationship ranked second in importance only to family relationships and was considered more important than relationships with coworkers, or spiritual and financial advisers.

"The patient-physician relationship is part of the critical underpinnings of stable societies."

In addition to diagnosis, treatment, and prevention, the relationship reinforces family linkages, processes daily fears and worries, and helps reinforce long term confidence and associated willingness to invest in the future.

Patients and doctors evaluated an ideal doctor's performance in "humanistic domains" (compassion, trust and understanding) and "access domains" (access to the doctor, amount of time spent, and access to a range of treatments). On average, doctors tended to score themselves higher in both domains than patients did by an average of 12 %. Patients in the USA thought there were greater opportunities for improvement in access.

BMJ September 13, 2003; 327: "News" reported by Stephen Pincock, BMJ staff, London.
www.bmj.com/cgi/content/full/327/7415/581

Comment:

It is still a privilege to be a physician. RTJ

==========

Herbal Doesn't Mean Insignificant…

9-14 EFFECT OF ST JOHN'S WORT ON DRUG METABOLISM BY INDUCTION OF CYTOCHROME P450 3A4 ENZYME

St. John's wort is a widely used over-the-counter herbal product. Recent multicenter, double-blind, placebo controlled studies did *not* support its effectiveness for moderate or severe depression.

A number of case reports and clinical studies have implicated it in a wide variety of drug interactions. The current study assessed the drug's ability to alter cytochrome P450 activity in healthy volunteers.

Conclusion: St John's wort significantly *induces* cytochrome P450 3A4 (CYP3A4) activity in the liver. This hastens the metabolism of at least half of all marketed medications.

STUDY

1. Open-label study involved 12 healthy volunteers, age 22 to 38.
2. At baseline, assessed cytochrome P450 (CYP) activity by two probe drugs: 1) 30 mg dextromethorphan [*Robitussin*] and 2) 2 mg alprazolam [*Xanax*; *Generic*]. Alprazolam is predominantly metabolized by CYP 3A4; dextromethorphan by CYP 2D6.
3. Subjects were then given 14 days of St John's wort (trade name, *Kira*) 300 mg three times daily.
4. At 14 days, participants were again given the two probe drugs to establish effect of St John's wort on their metabolism. The St John's wort was continued for another 2 days.

RESULTS

1. Metabolism of alprazolam after the second administration was greatly increased from baseline. Plasma clearance was increased two-fold. Half life was shortened from 12 hours to 6 hours. The increased degradation of the drug was attributed to induction of CYP 3A4. At 48 hours, no participant had measurable concentrations of alprazolam after St. John's administration, compared with 11 of 12 participants at baseline.
2. St. John's wort did not affect CYP 2D6 activity according to dextromethorphan metabolism.

COMMENT

1. Approximately 50% of all currently used medications are metabolized by cytochrome P450 3A4.
2. Long-term administration of St John's wort may diminish clinical efficacy and increase dosage requirements for a large and diverse group of medications. In this study, St John's wort substantially hastened metabolism of alprazolam by inducing activity of CYP 3A4
3. Single or short-term doses (less than 3 days) of St. John's wort have little effect of CYP 3A4.
4. Repeated dosing of St John's wort variably altered activity of CYP 2D6. In some patients plasma levels of dextromethorphan were increased , in some were decreased. The authors conclude that effects of St John's wort on CYP 2D6 are not likely to be of clinical significance.

CONCLUSION

Long-term dosing of St John's wort results in induction of CYP 3A4 and diminishes clinical effectiveness or increases dosage requirements of the 50% of drugs metabolized by this liver enzyme. St. John's wort can significantly alter the effectiveness and dosing of a wide range of medications.

JAMA September 17, 2003; 290: 1500-1504 Original investigation, first author John Markowitz, Medical University of South Carolina, Charleston, SC. www.jama.com

This article was initially abstracted by Coleman D Carter, M.D,

As the authors point out, the wide spread use of herbal medications can have a significant impact on medical therapy. Including these drugs on the patient's drug list and educating patients on their potential interactions is critical. CDC

Two editorials in this issue of JAMA comment:

Internet Marketing Of Herbal Products (pp 1505-09; first author Charles A Morris, Harvard Medical School)

Persons accessing information from the Internet are misled by vendor's claims that herbal products can treat, prevent, diagnose, and even cure specific disease, despite government regulations prohibiting such statements. Physicians should be aware of this widespread and easily accessible information. More effective regulation is required to put this class of therapeutics on the same evidence-based footing as other medicinal products.

Drugs, Alias Dietary Supplements (pp 1519-20; first author Catherine D DeAngelis, JAMA editor)

Once a dietary supplement is marketed, the onus is on the FDA to demonstrate that the product is unsafe, before it can take regulatory action. This amounts to a postmarketing regulatory system. "Disease claims are frequently made on the Internet despite the FDA ruling that these are not permitted." The preceding study adds to the growing literature on the biological actions and adverse effects of dietary supplements. Because many dietary supplements have or promote biological activity, they must be considered active drugs, and regulated as such. There are problems of lack of standardization, adulteration of botanical preparations, interactions between herbs and standard drugs, and lack of reporting of adverse effects.

Comment:

Snake oil salesmen, quacks, and charlatans now have modern technology to vastly increase their audience. It is amazing that some of the most educated people use "dietary supplements' and herbal medications, and believe in them. They seem totally oblivious to possible harmful effects. RTJ

Walking on sham…

9-15 EFFECT OF MAGNETIC VS SHAM-MAGNETIC INSOLES ON PLANTAR HEEL PAIN: A RANDOMIZED CONTROLLED TRIAL

A large number of people are using magnets to relieve their pain. US annual sales are estimated at $500 million. Studies supporting benefits of static magnet have had significant methodological flaws. The current study evaluates the effect of insole magnets on plantar fasciitis, a therapeutic use that has had little research.

Conclusion: Magnets did not benefit.

STUDY

1. Randomized, double-blind, placebo-controlled trial of 101 volunteer patients with plantar fasciitis of at least 30 days duration.
2. Randomized to daily use of 1) static magnets vs 2) sham magnets placed on insoles
3. Daily pain diaries were kept for at least 8 weeks.
4. Trial magnets were similar to those available on the market.

RESULTS

1. Comparison at 4 and 8 weeks showed no difference in a variety of pain assessment scores.
2. 44% of the nonmagnetic group versus 31% of the magnetic group were all or mostly better at 4 weeks. At 8 weeks, the numbers were 33% and 35%, respectively.
3. Morning pain intensity (range on 0 to 10 visual-analogue scale):

Follow-up interval	Non-magnetized	Magnetized
Baseline	6.9	6.9
4-week	4.2	4.4
8-week	3.9	3,9

4. Participants who believe a priori that magnets would be beneficial trended toward categorical improvement no matter which group they were actually in. This same group of participants (both non-magnetized and magnetized) had significantly more improvement in morning pain intensity at 8 weeks.

DISCUSSION

1. The strength of these magnets was comparable to widely available devices.
2. Although participants could have tested their insoles for magnets, they signed an agreement they would not. At the end of study an equal number guessed their correct group, which was no different than chance.

CONCLUSION

Static magnets are ineffective in the treatment of plantar heel pain.

JAMA September 17, 2003; 290: 1474-1478. Original investigation, first author Mark Winemiller, Mayo Clinic, Rochester, MN. www.jama.com

Article originally edited by Coleman D. Carter, M.D.

Objective observation is the appropriate tool to counter commercial exploitation of placebo delusions. CDC

Comment:

Patients improved over time equally in the 2 groups. Was this due to a placebo effect, natural history of the pain, or a benefit from the insole itself? RTJ

No Benefit

9-16 METHYLXANTHINES FOR EXACERBATIONS OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Several prestigious organizations recommend consideration of addition of oral or intravenous methylxanthines to aerosolized bronchodilators for severe exacerbations of COPD. Methylxanthines do produce several effects that may be beneficial to patients with stable COPD—bronchodilation, immunomodulation, reduction of diaphragmatic muscle fatigue, and increased mucociliary clearance.

Randomized trials, however, have been small and have produced conflicting results.

This meta-analysis asks--are methylxanthines, added to standard treatment of patients with acute exacerbations of COPD, really beneficial?

Conclusion: No

STUDY

1. Meta-analysis found 4 randomized trials meeting inclusion criteria (169 patients).
   COPD exacerbations were considered moderately severe—FEV_1 range 0.6 to 0.8.
2. All were treated in the emergency department or on admission to the hospital. Co-interventions were permitted—beta-agonists, ipratropium, antibiotics, corticosteroids, and oxygen.
3. Trials compared add-on oral theophylline and intravenous aminophylline with placebo.
4. Patients with asthma were excluded.
5. Main outcomes = mean change in spirometry, clinical end points, symptom scores, and adverse events.

RESULTS

1. Mean change in FEV1 and at 2 hours were similar between groups.
2. Non-significant reductions in admissions and length of stay were offset by non-significant increases in relapses at one week.
3. Changes in symptom scores did not reach significance.
4. Methylxanthines caused more nausea and vomiting than placebo (odds ratio = 4.6) and non-significant increases in tremor, palpitations, and arrhythmias.

CONCLUSION

When given in conjunction with other standard treatments, methylxanthines did not confer statistically significant benefits for lung function, clinical outcomes, and symptoms in patients with exacerbations of COPD. They significantly increase nausea and vomiting.

BMJ September 20, 2003; 327: 643-46 Original investigation, first author R Graham Barr, Columbia-Presbyterian Medical Center, New York. www.bmj.com/cgi/content/full/327/7416/643

Comment:

The article mentions that The American College of Physicians recommends against use of methylxanthines for exacerbations. A seminar in The Lancet September 27, 2003 states that the greater side-effect profile of theophyllines has relegated them to a third-line, add-on role in treatment. RTJ

Disappointing!

9-17 PARATHYROID HORMONE PLUS ALENDRONATE—A Combination That Does Not Add Up

The bisphosphonates, alendronate (*Fosamax*) and risedronate (*Actonel*), and the selective estrogen-receptor modulator raloxifene (*Evista*) belong to the class of antiresorptive drugs. They inhibit bone resorption and prevent further bone loss. Since bone formation and further mineralization continue for some time, these agents result in moderate increase in bone mineral density (**BMD**). Parathyroid hormone is the only agent that is capable of actually stimulating bone formation.

These classifications are an over simplification. Antiresorptive drugs do more than just inhibit bone resorption. Because bone formation is coupled with bone resorption, antiresorptive drugs eventually reduce bone formation. Overall bone turnover then decreases. Similarly, the bone formation stimulating regimen (intermittently administered parathyroid hormone) increases not only bone formation, but also bone resorption. The balance favors bone formation and bone mass increases.

Parathyroid hormone can have both catabolic and anabolic effects of the skeleton. Constant exposure to high levels of the hormone (during continuous infusion, and in patients with hyperparathyroidism) bone loss occurs. The loss is particularly high in cortical bone, such as the femoral neck and forearm. In contrast, when administered intermittently, as by daily injections, it has profound anabolic effects, particularly on trabecular bone (as in vertebrae). It also improves bone micorarchitecture, leading to an increase in bone strength that is independent of changes in BMD.

It would be plausible to assume that the effect of a bisphosphonate + parathyroid hormone would be additive, since their mechanisms of action differ. Unfortunately, this is not the case. Two studies in this issue of NEJM [1,2] reported that the combination did not lead to an increase in BMD. Actually, in the group assigned to parathyroid hormone alone, BMD increased more than in the group assigned to dual therapy. (Ie, with respect to trabecular bone at the spine, parathyroid hormone alone is better than combination therapy.) Apparently, alendronate impairs the anabolic activity of parathyroid hormone.

NEJM September 25, 2003; 349: 1277-78 Editorial by Sundeep Khosla, Mayo Clinic, Rochester, Minn.

1 "The Effects of Parathyroid Hormone and Alendronate alone, or in Combination in Postmenopausal Women" NEJM September 2, 2003; 349: 1207-15

2 "The Effects of Parathyroid Hormone, Alendronate, or Both in Men with Osteoporosis" NEJM September 2, 2003; 349: 1216-26 www.nejm.org

Comment:

Based on common sense, I would wager most primary care clinicians would have predicted an additive effect. Too bad it did not. RTJ