PRACTICAL POINTERS

FOR

PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

JUNE 1999

JAMA, NEJM, LANCET
BRITISH MEDICAL JOURNAL
ARCHIVES OF INTERNAL MEDICINE
ANNALS OF INTERNAL MEDICINE
ODDS AND ENDS

PUBLISHED BY PRACTICAL POINTERS INC.
EDITED BY RICHARD T. JAMES JR., M.D.
FIRST CHARLOTFE PHYSICIANS
300 BILLINGSLEY ROAD
CHARLOTTE NC 28211 USA

CLINICALLY APPLICABLE POINTS

THIS MONTH IN PRACTICAL POINTERS

6-1 THE LONG-TERM PROGNOSTIC SIGNIFICANCE OF REPEATED BLOOD PRESSURE MEASUREMENTS IN THE ELDERLY

This 10-year study found a strong, positive, continuous, and independent association in elderly people between total and cardiovascular mortality and systolic BP, but not diastolic BP.

Diastolic BP is still overstressed in the diagnosis and treatment of older patients.

Any benefit in treatment of hypertension in the elderly might be attributed more to lowering systolic BP than to lowering diastolic BP. Indeed, efficacy of therapy of isolated systolic hypertension is well documented.

6-2 EFFECT OF METOPROLOL CR/XL IN CHRONIC HEART FAILURE

This large international investigation reinforces the value of beta-blockade in treatment of heart failure. Dose — start low and go slow.

This applies mainly to class II and III HF. Applicability to class IV not certain.

6-6 GLYCEMIC CONTROL WITH DIET, SULFONYLUREA, METFORMIN, OR INSULIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

The UKPDS 49 study confirms that oral drug or insulin therapy (compared with diet alone) increases the likelihood that patients will attain a HbA1c below 7%, the level at which microvascular complications are less common. However, with time, diabetes control deteriorates due to progressive beta-cell dysfunction, and only a minority can be adequately controlled on monotherapy. The majority of patients require multiple therapies (oral + insulin) to maintain satisfactory glycemic control.

6-8 THE EFFECT OF LOW-DOSE CONTINUOUS ESTROGEN AND PROGESTERONE WITH CALCIUM AND VITAMIN D IN ELDERLY WOMEN.

Continuous half-dose conjugated equine estrogen combined with half-dose medroxyprogesterone is well tolerated and has the same bone-sparing effects as higher doses. This regimen may be more acceptable to some women.

6-9 THE EFECT OF RALOXIFENE ON RISK OF BREAST CANCER IN POSTMENOPAUSAL WOMEN.
6-10 TAMOXIFEN IN TREATMENT OF INTRADUCTAL BREAST CANCER.

A 3-year primary prevention study reports that the selective estrogen receptor modulator raloxifene reduced incidence of breast cancer by 75%.

The second study reports that tamoxifen adjuvant therapy improved prognosis in patients with DCIS.

The downside of SERMS is an increased incidence of thromboembolic disease and lack of benefit for hot flashes.

6-12 TRANS FATTY ACIDS AND CORONARY HEART DISEASE.
6-13 EFFECTS OF DIFFERENT FORMA OF DIETARY HYDROGENATED FATS ON SERUM LIPOPROTEIN CHOLESTEROL LEVELS.

Trans (hydrogenated) fatty acids should be eliminated from the "healthy diet". They produce the most unfavorable LDL-cholesterol/HDL-cholesterol ratio of any fatty acid. An average of 2% of calories as trans fats (about 4 g) would be predicted to account for

a substantial number of deaths from coronary heart disease. One doughnut contains almost that much; one serving of french fries about 2.5 times as much.

HIGHLIGHTS JUNE 1999

6-1 THE LONG-TERM PROGNOSTIC SIGNIFICANCE OF REPEATED BLOOD PRESSURE MEASUREMENTS IN THE ELDERLY.

The study found a strong, positive, continuous, and independent association in elderly people between total and cardiovascular mortality and systolic BP, but not diastolic BP.

This suggests that diastolic BP is still overstressed in the diagnosis and treatment of older patients.

Any benefit in treatment of hypertension in the elderly might be attributed more to lowering systolic BP than to lowering diastolic BP. Indeed, effectiveness of therapy of isolated systolic hypertension is well documented. Archives Int. Med. June 14,1999, 1203-12

6-2 EFFECT OF METOPROLOL CR/XL IN CHRONIC HEART FAILURE:The MERIT-HF Trial

Metoprolol controlled release/long-acting once daily in addition to optimum standard therapy improved survival in patients with stable chronic heart failure. Lancet June 12, 1999; 353: 2001-07

6-3 BENEFIT OF BETA-BLOCKERS FOR HEART FAILURE: Proven in 1999

"The benefit of beta-blocker treatment for heart failure is now certain and substantial and should be incorporated into modern practice guidelines." Lancet June 12, 1999; 353: 1988-89

6-4 GENERAL PRACTITIONERS' PERCEPTIONS OF EFFECTIVE HEALTH CARE

"The findings of our study suggest that the central assumptions of the evidence based medicine paradigm may not be shared by many general practitioners, making its application to general practice problematic."

"The suggested routes to practicing evidence-based medicine fail to comprehend the complex nature of general practice." BMJ June 5, 1999; 318:1532-35

6-5 LONG-TERM INTAKE OF DIETARY FIBER AND DECREASED RISK OF CORONARY HEART DISEASE IN WOMEN

High fiber intake, particularly from cereal sources, reduced the risk of CHD. JAMA June 2, 1999; 281: 1998-2004

6-6 GLYCEMIC CONTROL WITH DIET, SULFONYLUREA, METFORMIN, OR INSULIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS Progressive Requirement for Multiple Therapies (UKPDS 49)

Type 2 diabetes is characterized by a steady deterioration of glucose control over the years due to progressive beta-cell dysfunction. It becomes more difficult to attain near-normal glycemic control.

Compared with diet alone, insulin, sulfonylurea, or metformin as monotherapy increased by 2- to 3-fold the proportion of patients who attained HbA1c below 7%. However, the progressive deterioration of diabetes control was such that after 9 years only about 25% of patients could be controlled on monotherapy.

The majority of patients need multiple therapies to attain satisfactory glycemic control over the long-term. JAMA June 2, 1999; 281: 2005-12

6-7 FUNCTIONAL SOMATIC SYDROMES

"Functional somatic syndromes" (FSS) applies to several related syndromes characterized more by symptoms, suffering, and disability than by consistently demonstrable tissue abnormality. They include: multiple chemical sensitivity, the sick building syndrome, repetition stress injury, the side effects of silicone breast implants, the Gulf War Syndrome, chronic whiplash, chronic fatigue syndrome, irritable bowel syndrome, and fibromyalgia."

The article reviews causation, psychosocial factors, and management. Annals Int Med June 1, 1999; 130: 910-921

6-8 THE EFFECT OF LOW-DOSE CONTINUOUS ESTROGEN AND PROGESTERONE THERAPY WITH CALCIUM AND VITAMIN D IN ELDERLY WOMEN

Continuous oral administration of conjugated equine estrogen 0.3 mg/d and medroxyprogesterone 0.25 mg/d, combined with adequate calcium and vitamin D produced a significant bone-sparing effect in elderly women. The combination was well tolerated by most women. Annals Int. Med. June 1, 1999; 130: 897-904

6-9 THE EFFECT OF RALOXIFENE ON RISK OF BREAST CANCER IN POSTMENOPAUSAL WOMEN: Results of the MORE Randomized Trial

Among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 76% during 3 years of primary preventive treatment with raloxifene. JAMA June 16, 1999; 281: 2189-97

6-10 TAMOXIFEN IN TREATMENT OF INTRADUCTAL BREAST CANCER: National Surgical Adjuvant Breast and Bowel Project B-24 Randomised Controlled Trial

Tamoxifen, added to lumpectomy and radiation therapy, was more beneficial than lumpectomy plus radiation. Lancet June 12, 1999; 353:1993-2000

6-11 TAMOXIFEN HITS THE TARGET IN SITU

Tamoxifen reduces incidence of metastatic disease from breast cancer. It is effective in primary prevention of breast cancer. Now, effectiveness is reported for use in reducing recurrent DCIS. Lancet June 12, 1999; 353: 1986-87

6-12 TRANS FATTY ACIDS AND CORONARY HEART DISEASE

The adverse effect of trans fats on the LDL-c / HDL-c ratio is clinically significant. The average intake of 2% of calories as trans fat in the US wold be predicted to account for a substantial number of deaths from coronary heart disease. (2% of a 2000 cal diet = 40 cal = about 4 g fat. One doughnut contains 3.2 g trans fat; one large french fries, 10 g.) NEJM June 24, 1999; 340: 1994-98

6-13 EFFECTS OF DIFFERENT FORMS OF DIETARY HYDROGENATED FATS ON SERUM LIPOPROTEIN CHOLESTEROL LEVELS

The consumption of products low in trans fats and saturated fat has beneficial effects on serum lipoprotein cholesterol levels. NEJM June 24, 1999; 340: 40

6-14 GLUCOCORTICOID THERAPY FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Two studies concerning COPD in the issue of NEJM reported slight to moderate transient improvement in lung function with oral and inhaled corticoids.

At times patients with acute exacerbations of COPD will have increased numbers of eosinophiles in bronchial biopsy specimens. This may be caused by a respiratory virus infection which attracts eosinophiles and results in a more favorable response to corticosteroids. NEJM June 24, 1999; 340: 1990-91

6-15 EFFECT OF CIGAR SMOKING ON THE RISK OF CARDIOVASCULAR DISEASE, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, AND CANCER IN MEN.

Independent of other risk factors, regular cigar smoking can increase risk of coronary heart disease, COPD, and cancers of the lung and upper aero-digestive tract. NEJM June 10, 1999, 340: 1773-80

6-16 RECENT ADVANCES IN VARICELLA-ZOSTER VIRUS INFECTION

This article addresses molecular biology and immunology of the VZV; transmission; clinical features; and diagnosis; management of varicella, zoster, and postherpetic neuralgia; and prevention of varicella and zoster. Annals Int. Med. June 1, 1999; 130: 922-32

6-17 REHABILITATION OF HEMIPARESIS AFTER STROKE WITH A MIRROR

A novel approach to physiotherapy. Lancet June 12, 1999; 2053-54

6-18 STANDING STATISTICS RIGHT SIDE UP

Two articles in this issue of the Annals review the "P value" and Bayes theorem. The editor comments: "In our view, the articles will contribute importantly to the task of standing statistical inference right side up, We recommend it to our readers' most serious attention" Annals Int. Med. June 15, 1999; 130: 1019-21

6-19 OPTIMISATION OF ANTIHYPERTENSIVE TREATMENT BY CROSSOVER ROTATIONS OF FOUR MAJOR CLASSES

Essential hypertension is a heterogeneous disorder. It would be surprising if the variable pathogenesis did not cause detectable variability in individual responses to different agents.

There is a marked variability in hypertensive patients' response to different antihypertensive drugs. Optimization of treatment requires systematic rotation through several therapies. An AB/CD rule is proposed in which one of each of the two pairs is initially selected to abbreviate the rotation in routine practice. "We found significant variability in the response of most patients to the four main classes of antihypertensive agents. This variability was such that only a minority of patients were likely to receive their best drug first, or to reach a conventional target for blood pressure treatment without the process of systematic rotation. " Lancet June 12, 1999; 353: 2008-13

6-20 LABORATORY DIAGNOSIS OF VITAMIN B12 AND FOLATE DEFICIENCY

A Guide for the Primary Care Physician

"The accurate diagnosis of deficiencies is a complex task. No easily performed test can reliably serve as a diagnostic gold standard." Archives Int Med., June 28, 1999; 159: 1289-98

RECOMMENDED READING

6-4 GENERAL PRACTITIONERS' PERCEPTIONS OF EFFECTIVE HEALTH CARE

6-7 FUNCTIONAL SOMATIC SYDROMES

REFERENCE ARTICLES

6-16 RECENT ADVANCES IN VARICELLA-ZOSTER VIRUS INFECTION

6-18 STANDING STATISTICS RIGHT SIDE UP

6-20 LABORATORY DIAGNOSIS OF VITAMIN B12 AND FOLATE DEFICIENCY

6-21

6-1 THE LONG-TERM PROGNOSTIC SIGNIFICANCE OF REPEATED BLOOD PRESSURE MEASUREMENTS IN THE ELDERLY.

Systolic BP (SBP) tends to increase with age. Diastolic BP (DBP) tends to plateau or even decline after the fifth decade.1

Hypertension defined as SBP > 140 mm Hg and/or DBP > 90 is present in over half of subjects over age 65. Isolated systolic hypertension (ISH; SBP > 140 and DBP < 90) is the most common form. In one study in Italy, 4 of 5 elderly subjects over age 65 had a SBP > 140, and 1 in 3 had DBP > 90.

In young and middle-aged people, both SBP and DBP have a continuous, strong, and independent relationship with cardiovascular morbidity and mortality. This relationship is not well documented in the elderly.

This study assessed whether SBP and DBP are independent indicators of mortality in the elderly.

Conclusion: SBP, but not DBP, was a strong, positive, continuous, independent indicator of mortality risk in the elderly.

STUDY

1. Prospective observational cohort study analyzed long-term prognostic significance of repeated SBP and DBP measurements in 3854 persons over age 65 at baseline. (mean age = 73).
2. Subjects were randomly selected from general practices in Italy in 1983.
3. BP was measured at 2 initial visits 1 week apart and quarterly during the first year.
4. Follow-up = 10 years.

RESULTS

1. During 10-year follow-up: 41% died — about half of cardiovascular disease.
2. There was a positive, continuous, graded, strong, and independent association between cardiovascular mortality and total mortality with the baseline SBP.
3. But not with the baseline DBP.
4. The pattern was similar for both sexes and for both those younger and older than 75.
5. The pattern was similar regardless of whether or not the subjects had received antihypertensive treatment at baseline.2
6. There was no "J shaped" mortality curve. (Ie, the lowest BPs were not associated with excess mortality.)
7. Data were reanalyzed excluding deaths in the first 3 years to eliminate effect of illness and frailty at baseline. Results were the same.
8. Relative risk (RR) of cardiovascular mortality:

Systolic BP	< 140	140-159	160-179	≥180
RR	1.0	1.25	1.4	1.75

Diastolic BP	< 90	90-99	≥100
RR	1.0	1.2	1.0

(My estimates from figure 2 p 1208 RTJ)

DISCUSSION

1. In the elderly, a high systolic BP (> 140) as measured in general practice over 1 year was associated with a significant excess of total mortality and cardiovascular mortality over the following 10 years.
2. There was no association between high diastolic BP and mortality.
3. Antihypertensive drug treatment was prescribed to half the population at baseline. This did not change the adverse outcomes.2
4. Results did not change when deaths within the first 3 years of follow-up were excluded to avoid the confounding effect of short-term mortality due to co-morbidity.
5. There was no excess of deaths in the subgroups with lower DBP. (Ie, no "J shaped" curve.)

6. Systolic hypertension, particularly isolated systolic hypertension, is a condition (and a risk factor) more common in old age.

CONCLUSION

The study found a strong, positive, continuous, and independent association in elderly people between total and cardiovascular mortality and systolic BP, but not diastolic BP.

This suggests that diastolic BP is still overstressed in the diagnosis and treatment of older patients.

Any benefit in treatment of hypertension in the elderly might be attributed more to lowering systolic BP than to lowering diastolic BP. Indeed, efficacy of therapy of isolated systolic hypertension is well documented.

Archives Int. Med. June 14,1999, 1203-12 Original investigation by the "Studio sulla Pressione Arteriosa nell'Anziano" (SPAA), first author Claudio Alli, Ospedale Niguarda and the Instituto di Ricerche Farmacologiche, Milan, Italy.

An editorial in this issue of the Archives (pp 1165-66) comments: National surveys suggest that physicians and the public are not paying sufficient attention to control of systolic BP. The new targets are < 140 for most patients and less than130 for patients with diabetes and renal impairment, and less than 125 for those with proteinuria (> 1g/24 h).

Comment:

1. The adverse effects of a high SBP (with the resultant increase in pulse pressure (SBP minus DBP) is likely due to the effect of atherosclerotic stiffening of arteries. SBP is increased; DBP falls; pulse pressure increases. Indeed, an increased pulse pressure itself carries an adverse prognosis. This adds the risk of atherosclerosis to the risk of hypertension. Reducing SBP may decrease risk of morbidity and mortality even if the atherosclerotic process remains unchanged. Certainly, diastolic hypertension should not be neglected. But it is likely more of a risk factor in younger persons.
2. This is discouraging. I suspect the problem is lack of adequate treatment due to insufficient compliance and follow-up. We do know that many with hypertension are inadequately treated.

The data for this study was collected in "the real world" by the general practitioners. This adds to the strength and influence of the conclusions. RTJ

==========

6-2 EFFECT OF METOPROLOL CR/XL IN CHRONIC HEART FAILURE: The MERIT-HF Trial

Use of angiotensin-converting enzyme (ACE) inhibitors benefits patients with heart failure (HF). But, mortality remains high. Present standard therapy does not prevent sudden death, which constitutes a high proportion of deaths in patients with chronic HF.

Previous studies suggested that long-term therapy with beta-blockers improves hemodynamics and survival in HF.

This study asked, does the beta-blocker metoprolol [Lopressor], in addition to standard therapy, benefit patients with chronic HF?

Conclusion: Yes.

STUDY

1. Enrolled almost 4000 patients (mean age 64) with chronic HF (functional class II, III, and IV). All had ejection fractions less than 40% and were stabilized on standard therapy.
2. Randomized, double-blind to: 1) metoprolol controlled release/extended release (CR/XL) [Toprol-XL] or 2) placebo.
3. Starting dose was 12.5 mg (for class III and IV) and 25 mg daily (for class II).
4. Target dose was 200 mg daily up-titrated over 8 weeks.
5. Mean follow-up = 1 year. (Trial was discontinued early because of favorable outcome.)

RESULTS

1. All cause mortality treated group vs placebo (7% per patient-year vs 11% -- absolute difference = 4%; NNT(benefit-1-year) = 25.

2. There were fewer sudden deaths in the treated group (79 vs 132) and deaths from worsening HF (30 vs 58).

3. Benefits were evident within 1 to 3 months.

DISCUSSION

1. Once-daily metoprolol CR/XL added to optimum standard treatment (primarily ACE inhibitors and diuretics) lessened all-cause mortality by 34% in clinically stable patients with symptomatic chronic heart failure and lowered ejection fractions. (NYHA functional classes II-IV)

2. Treatment of 27 patients for 1 year can prevent one death.

3. Results were similar to those of the Cardiac Insufficiency Bisoprolol Study II (CIBIS II). Bisoprolol, like metoprolol, is highly beta-1 selective.

4. ACE inhibitors provide no protection against sudden death in patients with chronic HF.

5. The great majority of patients in this trial had mild to moderate HF (class II and III). These patients are more likely to die suddenly due to ventricular fibrillation, and less likely to die of progressive HF.

6. Class IV patients are more likely to die of progressive HF. Since there were few patients in this study with class IV HF, efficacy and safety of beta-blocker therapy in patients with severe HF remains to be assessed. Nevertheless, about a quarter of patients in this study died of worsening HF. Metoprolol significantly lowered risk of this cause of death.

7. Of interest – systolic BP was lowered less by metoprolol than by placebo. This supports the function of beta-blockers in improving left ventricular geometry and function.

8. Metoprolol CX/XL can be given once daily since action lasts over 24 hours. The mean dose achieved in the study was 159 mg daily.

9. The metoprolol was well tolerated when started at a low dose and uptitrated slowly over 2 months.

CONCLUSION

Metoprolol controlled release/long-acting once daily in addition to optimum standard therapy improved survival in patients with stable chronic heart failure.

Lancet June 12, 1999; 353: 2001-07 Large international investigation by the Merit-HF Study Group

Comment:

Metoprolol is a lipophilic beta-selective (cardioselective) antagonist. It has no intrinsic sympathomimetic activity. In patients with HF it improves cardiac function, left ventricular remodeling, and exercise capacity; and lessens symptoms. As with all beta-blockers, an initial negative inotropic effect necessitates a low starting dose and up-titration. The starting dose in this study for class II and III HF was about 1/8 the target dose.

Metoprolol itself is less expensive than carvedilol (a non-selective blocker), the first beta-blocker shown to be effective in treatment of HF. It is also available as a generic — but not in the CR/XL form.

Study was supported by Astra Hassle of Sweden. RTJ

==========

6-3 BENEFIT OF BETA-BLOCKERS FOR HEART FAILURE: Proven in 1999

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

Now, a little more than 10 years after ACE inhibitors were reported to improve survival in patients with heart failure (HF), the additional benefit of beta-blockers is proven.

Over the past 20 years, 24 randomized trials of beta-blockers in HF were reported. Most patients were also taking ACE inhibitors. Addition of beta-blockers consistently improved left ventricular function. A meta-analysis showed the mean annual mortality was reduced from 9.7% to 7.5%. [NNT(benefit-1 year)= 50]

MERIT-HF study, the largest yet, reported a similar reduction in mortality. (Annual mortality reduced from 11% to 7.2%.) There were significant reductions in both sudden deaths and deaths from worsening HF. The trial indicated an unusually high cost-effectiveness.

ACE inhibitors improve symptoms, hemodynamics, ventricular remodeling, and survival. They primarily benefit by reducing death from worsening HF. There is no clear evidence that ACE inhibitors reduce sudden death.

The patients selected for recent beta-blocker trials generally have been relatively young, predominantly male, and had left ventricular systolic dysfunction. A high proportion of patients with HF in the community are older and have co-existing disorders. The benefit of beta-blockers in this type of patient is not known. For older patients adverse effects may be more common.

Which beta-blocker to use? The predominant effect is most probably a class effect. Thus, for the present, treatment with several drugs can be recommended. (Cost may be determining.)

"Patients with clinically stable heart failure and left-ventricular systolic dysfunction established on standard treatment, should be considered for beta-blocker therapy. Contraindications should be carefully observed. "

"The benefit of beta-blocker treatment for heart failure is now certain and substantial and should be incorporated into modern practice guidelines."

Lancet June 12, 1999; 353: 1988-89 Editorial by Norman Sharpe, Auckland Hospital, New Zealand.

==========

Recommended Reading

6-4 GENERAL PRACTITIONERS' PERCEPTIONS OF EFFECTIVE HEALTH CARE

Awareness of the latest scientific evidence and the ability to critically appraise the applicability of this evidence are crucial ingredients missing in everyday medical practice.

Evidence based medicine has emerged as a new paradigm. It is assumed that practitioners regard clinical effectiveness as a priority and will be keen to act in a way that optimizes this – that is, to identify shortcomings in their practice and change in line with scientifically valid evidence.

This study explored general practitioners' perceptions of the extent to which emphasis on clinical effectiveness is congruent with their thinking and behavior. What are general practitioners' perceptions of effective health care? Do they always practice effectively? If not, why not ?

Conclusion: Application of evidence based medicine in general practice is problematic.

STUDY

1. Qualitative study interviewed 24 general practitioners.
2. Respondents were asked to define effective health care. Were they practicing effectively according to their own criteria? What were the sources used to answer clinical questions about patients? What were the reasons for making changes in clinical practice?

RESULTS

1. Only one respondent thought he always practiced effectively.
2. Reasons for not practicing effectively:
    A. Doctor-related reasons:
        Self-perceived shortcomings in knowledge, experience, and skills.
        Pressure from conflicting ideas. ("You really don't know if you are right or wrong")

Being stressed or unmotivated.

B. Patient related reasons:

Presenting more than one problem – necessary to prioritize. (Evidence based entry requirements focus on one problem)

Patient non-compliance.

C. Doctor and patient-related reasons:

Differing cultural backgrounds, beliefs, and attitudes.

Demanding therapy the doctor deems ineffective. (Eg, antibiotics for colds.)

Requesting inappropriate investigations and referrals. (Doctors wanting to avoid conflict and to keep the "custom" of their patients.)

Depending on the placebo effect, even though it is considered "ineffective".

Feelings of sympathy for patients. (Eg, prescribing an "ineffective" drug for a sick child to relieve some of the suffering of the parents.)

Doctor's personal prejudices leading to spending less time or ignoring certain "difficult" patients.

D. Environmental reasons (Factors extraneous to both doctor and patient):

Time. ("Time influences everything. It influences getting a history correctly, engaging with the patient if you don't know them well, building up some sort of rapport, discussing treatment options, examining them properly.")

Lack of time may lead physicians to bow to inappropriate patient demands.

Lack of resources.

E. How do doctors source information?

All respondents mentioned a practice partner or specialist. Recourse to literature (books, journals, library) mentioned by about half; internet by 2; Medline by 1.

F. Changes in Clinical Practice:

Almost all had changed their practice over the past few years, most recalling up to 3 changes – using a different drug, a new test, or lowering treatment threshold.

The main reasons included for change were: contact with a specialist (6 changes), journal articles (5), scientific meetings (4).

DISCUSSION

1. "The findings of our study suggest that the central assumptions of the evidence based medicine paradigm may not be shared by many general practitioners, making its application to general practice problematic."

2. Respondents seemed acutely aware of, and sensitive to, patient's expectations. They were inclined to judge their practice in terms not only of clinical outcome, but also of a patient-centered interpretation of quality. Where requirements of clinical effectiveness openly clash with the preferences or circumstances of individual patients, the latter might take precedence. This concurs with theories on the "holistic" nature of general practice in which biomedical, personal, and contextual perspectives converge in decision making. "The linear decision making suggested by the model of evidence based medicine informed mainly by normative standards of clinical effectiveness, sits uneasily within this framework."

3. "In general practice, the doctor-patient encounter is a dynamic phenomenon underpinned by negotiation that takes account of the preoccupations of both parties. The fact that the doctor sometimes chooses to place more weight on the patient's agenda than on clinical evidence seems to be a rational strategy aimed at maintaining an important relationship. The maintenance of this relationship, which is likely to impact on the 'healing process' may be more important than staying within the bounds of a statistically defined consensus of clinical effectiveness."

4. There is increasing literature on the shortcomings of the evidence-based medicine model in general practice, including the scope and nature of the evidence available and its limited applicability in patient care. General practitioners may not share evidence-based medicine's overarching concern for clinical effectiveness, but instead see it as only one consideration in a wider framework that also takes account of service oriented concerns such as patient satisfaction and time management.

5. "Diagnosis by prognosis" and "diagnosis by therapeutic response", both common in the uncertain environment of general practice, may preclude the formulation of clear clinical questions demanded by the evidence based medicine model.

6. "The suggested routes to practicing evidence-based medicine fail to comprehend the complex nature of general practice."

CONCLUSION

The central assumptions of the evidence based medicine paradigm may not be shared by many general practitioners, making its application in general practice problematic. Promotion of effective care in general practice requires a broader vision and a more pragmatic approach which takes into account practitioners' concerns and is compatible with the complex nature of their work.

BMJ June 5, 1999; 318:1532-35 Original investigation and commentary, first author Zelda Tomlin, Royal Free and University College Medical School, London

Comment:

Compared with quantitative studies, qualitative studies are more difficult to abstract. They are less structured.

Evidence based medicine attempts to bring a degree of perfection into an imperfect world. There are large grey areas — gaps filled with uncertainty. Criteria of randomized trials exclude large segments of patients— more decline to be included even if eligible, more withdraw. Doubt remains for the many individual patients for whom the available evidence does not fit. One way of judging applicability of an evidence-based intervention is to compare: (A) the number of individuals originally contacted for the study; + (B) the number removed by exclusion criteria; + (C) the number withdrawing or not completing the study with (D) the number completing the trial. If the ratio of A + B + C / D is large, applicability to an individual patient in primary care may be limited.

There is a large gap between the "science" of medicine which focuses on a large, select group of individuals with a single, defined problem, and the "art" of medicine which focuses on an individual, often with co-morbidity, who may fit poorly, or not at all, into the application of the "science".

Even if the evidence could apply to an individual, there are economic, social, and cultural blockers, especially in primary care practice. Evidence based medicine applies more neatly to specialty care, where there are fewer variables.

Nevertheless, general practitioners do indeed change their practice to include new applications of the evidence. Almost all sought new information, especially from colleagues.

Evidence based medicine has power, but application is limited. RTJ

==========

6-5 LONG-TERM INTAKE OF DIETARY FIBER AND DECREASED RISK OF CORONARY HEART DISEASE IN WOMEN

High intake of dietary fiber, especially soluble fiber, decreases low-density lipoprotein cholesterol. It has little effect on high density lipoprotein cholesterol.

This study examined the association between long-term fiber intake in women on the incidence of coronary heart disease (CHD) in women.

Conclusion: High fiber intake in women was associated with reduced risk of CHD.

STUDY

1. The Nurses' Health Study prospectively followed over 68 000 women for up to 10 years.

2. All were free of diagnosed CHD, stroke, cancer, hypercholesterolemia, and diabetes at baseline.

3. Documented fiber intake by a validated food-frequency questionnaire.

RESULTS

1. The lowest quintile total fiber intake = 11 g/d; the highest = 23 g/d. For cereal fiber— 2g and 8 g.

2 Documented 591 major CHD events over the 10 years.

3. Age-adjusted relative risk for CHD by quintiles:

A. Highest quintile total fiber intake vs lowest = 0.77 after controlling for age and other factors.

(CI = 0.57-1.04)

B. Highest quintile cereal fiber intakes vs lowest = 0.63 (CI = 0.49-0.81).

4. Among different sources of dietary fiber (eg, fruit, vegetables, cereal), only cereal fiber was strongly associated with reduced risk.

5. For each 5 g/d increase in cereal fiber there was a 37% decrease in incidence of CHD.

DISCUSSION

1. There was a significant inverse association between intake of fiber and risk of CHD.

2. The association was confined to fiber from cereal sources.

3. The association was not explained by higher intakes of vitamins, vegetables, or fruits.

4. Results were concurrent with the large Health Professionals Follow-up Study of men.

5. Fiber reduces LDL-cholesterol through increased bile acid excretion and decreased hepatic synthesis. "However, based on a recent meta-analysis of 20 trials of high doses of all bran (rich in soluble fiber) the magnitude of the cholesterol-lowering effect was relatively small."

6. The CHD-reducing effect of cereal fiber was larger than would be expected from the observed decreases in cholesterol. Thus, other mechanisms are probably involved. (Eg, increasing insulin sensitivity and lowering triglyceride levels.)

CONCLUSION

High fiber intake, particularly from cereal sources, reduced the risk of CHD.

JAMA June 2, 1999; 281: 1998-2004 Original investigation, first author Alicja Wolk, Karolinska Institute, Stockholm, Sweden.

==========

6-6 GLYCEMIC CONTROL WITH DIET, SULFONYLUREA, METFORMIN, OR INSULIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS: Progressive Requirement for Multiple Therapies (UKPDS 49)

A goal in the treatment of diabetes is to produce near-normal glucose levels to prevent development of microvascular complications. Epidemiological studies suggest that when fasting glucose levels are held below 140 mg/dL (7.8 mmol/L) the risk of microvascular complications is lowered.

Risk increases at a HbA1c level above 7.0%. (Normal range 4.5% to 6.2%).

This study asked — how often can monotherapy with the above treatments achieve good control over time?

Conclusion: Not often.

STUDY

1. Multicenter, randomized, controlled trial entered over 4000 patients with newly diagnosed type 2 diabetes. Median fasting plasma glucose (FPG) = 207 mg/dL (11.6 mmol/L) and HbA1c = 9.1%

2. Placed on a low-fat, high carbohydrate, high fiber diet for 3 months, then randomized to: 1) continued diet alone, 2) insulin alone, 3) sulfonylurea alone, or 4) metformin alone for obese patients. Doses were considered maximum. (Insulin was once-a-day long-acting + regular if needed; See text p 2006)

3. Goal — to determine the proportion of patients achieving a target of HbA1c below 7%, or a FPG less than 140 mg/dL.

4. Follow-up every 3 months for 3, 6, and 9 years. A second or third therapy was added as necessary to maintain good control.

RESULTS

1. The proportion of patients who maintained target glycemic levels declined markedly over 9 years.

2. The proportion of those maintained on monotherapy over the 9 years:

	To achieve FBG below 140	HbA1c < 7%
Diet alone 8%	9%	
Insulin alone	42%	28%
Sulfonylurea alone	24%	24%
Metformin alone	18%	13%

3. Younger patients, the more obese, and those who were more hyperglycemic at baseline were less likely to achieve targets and to require multiple therapies.

DISCUSSION

1. Type 2 diabetes is characterized by a steady deterioration of glucose control over the years due to progressive beta-cell dysfunction. It becomes more difficult to attain near-normal glycemic control.

2. By 9 years, about 75% of patients will need multiple therapies to achieve FPG less than 140 mg/dL or HbA1c less than 7%.

3. One subset of patients on maximum sulfonylurea had metformin added. After 3 years the proportion of patients achieving HbA1c below 7% increased from 21% with sulfonylurea alone to 33% with the combination.

4. "It is apparent by 9 years after diagnosis even with this combination of oral agents, a substantial number, perhaps the majority, of patients will need the addition of insulin therapy to obtain an HbA1c level below 7%. The progressive decline in beta-cell function will require considerably greater use of insulin therapy than is currently prescribed."

5. While thiazolidines are an additional oral agent that can be used, in clinical practice they have similar efficacy to sulfonylureas or metformin and are unlikely to prevent the increasing hyperglycemia or to postpone need for insulin for more than a few years.

6. Although insulin therapy was better than oral drugs in reducing FPG concentrations, it was not as effective in reducing HbA1c as might have been anticipated. This is partly because oral agents reduce the postprandial as well as the fasting glucose, whereas a basal insulin supply only reduces the basal glucose concentrations. Adding soluble insulin to cover meals can lead to hypoglycemia and limit the degree to which near-normal glycemia can be attained.

7. Achieving HbA1c levels below 7% with insulin alone requires high doses, often well above 100 U/d, and is successful only in small groups of obese patients receiving detailed attention over a short period.

CONCLUSION

Compared with diet alone, insulin, sulfonylurea, or metformin as monotherapy increased by 2- to 3-fold the proportion of patients who attained HbA1c below 7%. However, the progressive deterioration of diabetes control was such that after 9 years only about 25% of patients could be controlled on monotherapy.

The majority of patients need multiple therapies to attain satisfactory glycemic control over the long-term.

JAMA June 2, 1999; 281: 2005-12 Original investigation by the United Kingdom Prospective Diabetes Study group, first author Robert C Turner, Radcliffe Infirmary, Oxford, England.

Recommended Reading

6-7 FUNCTIONAL SOMATIC SYDROMES

"Functional somatic syndromes" (FSS) applies to several related syndromes characterized more by symptoms, suffering, and disability than by consistently demonstrable tissue abnormality. They include: multiple chemical sensitivity, the sick building syndrome, repetition stress injury, the side effects of silicone breast implants, the Gulf War Syndrome, chronic whiplash, chronic fatigue syndrome, irritable bowel syndrome, and fibromyalgia."1

Patients with these syndromes have explicit and highly elaborate self-diagnoses. Their symptoms are often refractory to reassurance, explanation, and standard treatment of symptoms. FSS causes great suffering, distress, and carries substantial societal costs.

Rates of co-occurrence are high; epidemiological characteristics similar. Prevalence of psychiatric co-morbidity is higher than expected. Although discrete pathophysiological causes may ultimately be found in some patients, their suffering is exacerbated by a self-perpetuating, self-validating cycle in which common endemic somatic symptoms are incorrectly attributed to serious abnormalities. This reinforces their belief that they have serious disease.

Four psychosocial factors propel the cycle of symptom amplification:

1. Belief that one has a serious disease.
2. Expectation that the condition is likely to worsen.
3. The "sick role", including effects of litigation and compensation.
4. The alarming portrayal of the condition as catastrophic and disabling.

The climate surrounding functional somatic syndromes includes sensationalized media coverage, profound suspicion of medical expertise and physicians, mobilization of parties with a vested self-interest in the status of FSS, litigation, and a clinical approach that overemphasizes the biomedical and ignores psychosocial factors.

All of these influences exacerbate and perpetuate the somatic distress of FSS, heighten fears and pessimistic expectations, prolong the disability, and reinforce the sick role.

How should clinicians try to help patients with FSS? The author presents a six-step strategy:

1. Rule out diagnosable medical disease.

Remember the adverse effects of overly aggressive investigations which may foster the sick role and lead patients to expect a definitive medical explanation for all somatic distress. Be cautious in ordering tests and obtaining specialty consultations solely to reassure the patient. Negative findings provide little reassurance to most patients with FSS and often heighten rather than assuage anxiety. Extensive testing carries the risk of iatrogenesis and solidifies the patient's conviction that the distress has a biomedical cause.

2. Search for psychiatric disorders.

Particularly major depression and panic disorder. Both are highly prevalent and treatable. The likelihood of a psychiatric disorder increases linearly with the number of somatic complaints. But, patients must be reassured that their somatic symptoms are in no way imaginary or feigned. Reassure by telling them that psychiatric disorders are regarded less as causes of somatic symptom than as amplifiers that exacerbate and perpetuate symptoms.

3. Build a collaborative alliance with the patient.

This is crucial. Take care to acknowledge and legitimize the patient's suffering even though definitive bio-medical explanation has been elusive. Discourage assumption of the sick role and reduce alarming expectations about the clinical course.

4. Make restoration of function the goal of treatment.

Make symptom palliation, coping, and rehabilitation the focus of clinical enterprise. Focus is on coping rather than curing, on improving functional status rather than eradicating symptoms. Patients must be actively involved in the treatment process and must be dissuaded from assuming a passive role and waiting to be cured by medical procedures or interventions. Set realistic incremental goals. Encourage resumption of activities and return to work as much as possible.

5. Provide limited reassurance.

Reassure that grave medical diagnoses have been ruled out. Tell clearly that they do not have a lethal or progressive disease. But, because these patients feel ill and symptomatic, tell them what they do have, and not only what they do not have. Describe the process of amplification whereby sociocultural and psychological processes exacerbate distress and hinder recovery. Although this does not provide a definitive etiologic explanation for the distress, such a discussion gives patients an explanatory model that focuses on process and functioning rather than on structural abnormalities.

6. Prescribe cognitive-behavioral therapy for patients who have not responded to steps 1-5.

It can be effective therapy. It helps patients cope with symptoms when they examine their expectations and explore the effects of stress and distress and of the sick role

on their symptoms. It helps patients seek alternative explanations for symptoms, restructure faulty disease beliefs, alter expectations, and learn techniques of focused attention and distraction. It stimulates a more active role in coping and rehabilitation and counters the assumption that cure results only from application of technical interventions to passive patients.

Annals Int Med June 1, 1999; 130: 910-921 Review article by Arthur J Barsky and Jonathan F Borus, Brigham and Woman's Hospital, Boston. Mass.

Comment:

1. Is there a difference between patients with functional somatic syndromes and patients usually labeled as "somatizers"? There is a large overlap. Approach to management is similar:

A. Don't blame the patients or make him or her feel devalued or guilty. Understand and accept the patient's suffering.

B. Recognize uncertainty. We do not know the exact cause of the symptoms. No tests are available to determine cause. It may be that there is something in patients' nervous system which makes them more sensitive to pain and other symptoms.

C. Limit referrals and iatrogenic harm.

D. Reassure — life will go on. Despite your symptoms, there is no serious abnormality which will shorten life.

E. The goal is to help the patients cope and improve functioning. We cannot remove all disability. Many patients with disabilities live with discomfort and still lead productive and meaningful lives. Direct attention to care rather than cure. RTJ

==========

6-8 THE EFFECT OF LOW-DOSE CONTINUOUS ESTROGEN AND PROGESTERONE THERAPY WITH CALCIUM AND VITAMIN D IN ELDERLY WOMEN

The severity of side effects of long-term hormone replacement therapy (HRT) is dose related. Side effects limit acceptance by many women.

This study hypothesized that low doses of estrogen/progesterone would be more acceptable and achieve the same benefits in preventing osteoporosis as conventional doses.

Conclusion: Continuous low dose HRT, combined with calcium and vitamin D, provided the same bone-sparing effect as higher doses. The combination was well tolerated.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered 128 healthy white women over age 65. (mean = 73).

2. All had low bone mass (spinal bone mineral density under 0.91 g/cm2.)

3. Randomized to: 1) conjugated equine estrogen 0.3 mg/d + medroxyprogesterone 0.25 mg/d, or 2) matching placebos

4. In both groups, calcium supplementation was given to provide total intake above 1000 mg/d and supplemental 25-hydroxyvitamin D was given to bring serum levels to at least 75 nmol/L

5. Follow-up to 3 1/2 years.

RESULTS

1. Bone mineral density at 3 1/2 years (estimated from figure 2 p 900):

	Treated group	Placebo group
Spine (among those with 90% compliance)	+4.6%	-0.57%
Total body	+3.1%	-1%
Forearm	+1.5	-0.5%
Femoral neck	+1.6%	0

2. Among those who adhered to therapy, femoral neck bone mineral density increased by 0.62% per year4.

3. Biochemical markers (alkaline phosphatase, osteocalcin, and hydroxyproline) favored the treatment group.

4. Adverse effects: Symptoms related to HRT (breast tenderness, spotting, pelvic discomfort, and mood changes were mild and short-lived. Ten patients dropped out of the placebo group vs 11 in the treatment group. Most in the treatment group dropped out because of symptoms thought to be related to the HRT.

5. Most of the side effects associated with continuing HRT disappeared within 6 months.

6. Spine X-rays revealed 3 incident vertebral fractures in the treated group vs 4 in the placebo group.

DISCUSSION

1. Over a 3-year period, continuous oral administration of conjugated equine estrogen 0.3 mg/d and medroxyprogesterone 0.25 mg/d, combined with adequate calcium and vitamin D, produced a significant bone-sparing effect in elderly women.

2. At least 90% of women adhered to the regimen for 3 1/2 years.

3. Losses of bone in the placebo group were not significant over the 3 1/2 years, possibly due to the calcium and vitamin D supplementation.

4. Adverse effects of the low-dose HRT were generally short-lived and were not particularly severe.

5. The authors admit the results (bone mineral density) are surrogate for fracture, the real clinical endpoint.

CONCLUSION

Continuous oral administration of conjugated equine estrogen 0.3 mg/d and medroxyprogesterone 0.25 mg/d, combined with adequate calcium and vitamin D produced a significant bone-sparing effect in elderly women. The combination was well tolerated by most women.

Annals Int. Med. June 1, 1999; 130: 897-904 Original investigation, first author Robert R. Recker, Creighton University, Omaha, Nebraska.

Comment:

This strengthens the view that continuous estrogen-progestagen can be accepted by most women. The adverse effects, especially spotting, wane over time.

Is low-dose an advantage? It may be a selling point for some women. Those who cannot tolerate a standard dose might be willing to try the lower dose.

Certainly vitamin D and calcium should be added for all elderly women.

The problem of a substitute end-point remains. It may be reassuring for some women and physicians. Determining the fracture rate is much more of clinical interest. RTJ

==========

6-9 THE EFFECT OF RALOXIFENE ON RISK OF BREAST CANCER IN POSTMENOPAUSAL WOMEN: Results of the MORE Randomized Trial

Post menopausal women with high serum concentrations of estradiol have the highest risk of breast cancer (BC). Tamoxifen [Nolvadex] inhibits action of estrogen on breast tissue. It improves disease-free survival among women with estrogen-receptor positive BC, and reduces risk of contralateral BC. It however, increases thromboembolic disease and endometrial cancer.

Raloxifene [Evista]is also a selective estrogen receptor modulator, chemically distinct from tamoxifen and estradiol. It has antiestrogenic effects on breast and endometrium; and estrogenic effects on bone (beneficial), and lipids (beneficial), and blood clotting (harmful).

This study analyzed effects primary prevention by raloxifene on rates of BC over 3-years follow-up.

Conclusion: Among postmenopausal women, primary preventive treatment with raloxifene was associated with a 76% decrease in risk of invasive BC.

STUDY

1. Multicenter study entered over 7000 postmenopausal women (mean age 67).
2. All had osteoporosis defined by presence of vertebral fractures, or a bone density score of at least 2.5 SD below mean for young healthy women. Almost all were white.
3. None had history of BC.
4. Randomized to: 1) raloxifene 60 or 120 mg/d, or 2) placebo. Follow-up = 3 years.

RESU;TS

1. Thirteen cases of BC were confirmed among 5129 women in the treatment group (about 1 in 500) vs 27 among 2576 in the placebo group (about 1 in 100).
2. Relative risk = 0.24 (CI = 0.13 – 0.44)
3. To prevent one case of BC, 126 women would need treatment for 3 years.
4. The decrease was primarily on incidence of estrogen receptor-positive BC.
5. In the treatment group venous thromboembolism occurred in 0.7%; pulmonary embolism in 0.3%.
   RR = 3 compared with placebo.
6. No increased risk of endometrial cancer.
7. Adverse effects: Hot flashes, influenza-like syndromes, endometrial cavity fluid, peripheral edema, and leg cramps were more common. (Few women discontinued therapy for these reasons.)
   Thirty three in the raloxifene group withdrew due to hot flashes vs 2 in the placebo group.
8. No difference in vaginal bleeding and breast tenderness.

DISCUSSION

1. Primary prevention treatment with raloxifene was associated with a 76% reduction in risk of BC over a median of 40 months in postmenopausal women. This was attributed entirely to a reduction in estrogen receptor-positive cancer.
2. This supports the concept that raloxifene acts by interacting with estrogen receptors in the breast.
3. Further study is needed to compare effects of tamoxifen with raloxifene.
4. "Because breast cancer generally requires several years to grow to a clinically or radiographically detectable size, the cancers that were diagnosed during this trial were probably present when the study began. Therefore, the reduction in the risk of breast cancer within the first 40 months of treatment with raloxifene probably represents suppression or regression of subclinical cancer."
5. Tamoxifen, raloxifene, and estrogen increase risk of venous thromboembolism to a similar degree. (The risk is less than 1 patient in 100 over 3 years.) Nevertheless, women with a history of venous thromboembolism should not take these drugs.

6. Women taking these drugs should discontinue before any major surgery or immobilization.

7. Although not a concern of this study, the authors comment that raloxifene decreases LDL-cholesterol (beneficial) without altering HDL-cholesterol levels. It also is associated with decreasing bone turnover and risk of vertebral fractures.

CONCLUSION

Among postmenopausal women with osteoporosis, the risk of invasive breast cancer was decreased by 76% during 3 years of primary preventive treatment with raloxifene.

JAMA June 16, 1999; 281: 2189-97 Multiple Outcomes of Raloxifene Evaluation (MORE) Trial, original investigation, first author Steven R Cummings, Preventive Sciences Group, San Francisco, CA.

An editorial in this issue (pp 2243-44) "Encouraging News from the SERM Frontier comments:

Selective Estrogen Receptor Modulators are arousing intense interest. They bring the hope that in the future one may be developed that confers all the benefits of estrogen, and none of its risks. The first widely used, tamoxifen, has the undesirable effects of increasing hot flashes, endometrial cancer, and thromboembolism. The second generation drug, raloxifene has the beneficial effects of tamoxifen, but has not been associated with increased risk of endometrial cancer. Now it appears that it decreases risk of breast cancer. Cautious interpretation is needed — the trial lasted only 3 years. For women who are at risk of breast cancer who are considering estrogen therapy, raloxifene may be a welcome alternative. But, a big drawback of the currently available SERMs is that they do not relieve menopausal symptoms.

"Raloxifene should not be considered suitable for use by most women at this time, but its contributions to knowledge intensify the anticipation of finding something even better on this new frontier."

Comment:

The main drawbacks of raloxifene are two: venous thromboembolism and increase in hot flashes. The main advantage over estrogen is a breast cancer sparing-effect (vs the promoting effect of estrogen). Estrogen has the advantage of relieving menopausal symptoms.

==========

6-10 TAMOXIFEN IN TREATMENT OF INTRADUCTAL BREAST CANCER: National Surgical Adjuvant Breast and Bowel Project B-24 Randomised Controlled Trial

Before mammography, fewer than 3% of newly diagnosed breast cancers (BC) were ductal carcinoma in situ (DCIS). Most presented as large palpable masses, many with microinvasion. Now 20-30% of mammographically detected cancers are DCIS. For these patients, treatment with lumpectomy plus radiation therapy is more effective than lumpectomy alone. Because of the low recurrence rate of ipsilateral invasive cancer mastectomy is not warranted in these patients.

This trial asked – is lumpectomy + radiation therapy + tamoxifen [Nolvadex] more beneficial than lumpectomy + radiation therapy.

Conclusion: It is.

STUDY

1. Randomized, controlled trial entered over 1800 women with DCIS. Most did not have a palpable mass. Included some with resected margins involved with tumor.

2. Randomized to: 1) Group A –lumpectomy + radiation therapy + tamoxifen (20 mg daily for 5 years) or 2) Group B – lumpectomy + radiation therapy.

3. Median follow up = 6 years.

RESULTS

1. Women in the tamoxifen group had fewer cancer events at 5 years – 8.2% vs 13.4% Absolute difference = 5.2%. [NNT(benefit-5-years) = 19]

2. Cumulative incidence of all invasive breast cancer events = 2.1% in the ispsilateral breast; 1.8% in the contralateral breast; and 0.2% at regional or distant sites.

3. 224 patients had positive sample margins. In this group, ipsilateral cancer occurred at a rate of 17 per 1000 per year in group A and 31 per 1000 patients per year in group B

4. Comedonecrosis was present in 433 patients. In this group, ipsilateral cancer occurred at a rate of 19 per 1000 per year in group A and 27 per 1000 patients per year in group B.

5. Adverse effects: Overall toxicity was similar in both groups. No significant difference in phlebitis/thromboembolism and mood changes. Menstrual disorders, hot flashes, fluid retention and vaginal discharge were more common in the tamoxifen group. Endometrial cancer group A = 1.55; group B = 0.5%

DISCUSSION

1. Women with DCIS treated with lumpectomy + radiation therapy showed additional benefit from tamoxifen. The advantage was mainly due to a decrease in incidence of invasive cancer in the ipsilateral breast. The rates of invasive and non-invasive tumors in the contralateral breast and at distant sites also decreased.

2. "Our findings could contribute to the decision-making process about treatment of patients with mammographically detected DCIS when radiological or pathological evidence suggests that all the cancer was not removed after lumpectomy. Currently, mastectomy is commonly deemed appropriate when scattered calcifications are seen radiographically or more than one focus of clustered calcifications persist after surgery, when radiologists are uncertain about whether findings are indicative of invasive cancer, or when a tumor is at or close to a margin."

3. The findings suggest that use of tamoxifen could lead to more frequent avoidance of mastectomy.

CONCLUSION

Tamoxifen, added to lumpectomy and radiation therapy, was more beneficial than lumpectomy plus radiation.

Lancet June 12, 1999; 353:1993-2000 Original investigation, first author Bernard Fisher, Allegheny University of the Health Sciences, Pittsburgh, PA

Comment:

Tamoxifen is an antiestrogen which competes with estrogen for binding sites in target tissues, including the breast. RTJ

==========

6-11 TAMOXIFEN HITS THE TARGET IN SITU

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

Is there anything tamoxifen cannot do? Its activity in metastatic BC, for which tumor response rates may be about 40%, encourages use at an earlier stage of the disease. It is now standard adjuvant treatment for women with early BC. Overviews suggest that the scope and effectiveness of the drug as an adjuvant have been underestimated. Used properly (ie, for a duration of at least 5 years in tumors positive for estrogen receptors) it is associated with a reduction in the risk of recurrence approaching 50%. The notion that it is less effective in premenopausal women is wrong.

The same adjuvant trials show a 40% reduction in the risk of cancer in the opposite breast.

A 1998 primary prevention study (13 000 women) of tamoxifen vs placebo, reported 40% fewer BCs in the treated group. "Although the issue of primary prevention remains complex and unresolved, clearly in some women tamoxifen can prevent or delay the onset of breast cancer."

Now effectiveness is reported for use as an adjuvant in reducing risk of recurrent DCIS.

Mammography screening has made diagnosis of DCIS common. Not all BCs are preceded by DCIS, and not all DCISs lead to invasive cancer. Nevertheless, there is a small but real chance that invasive cancer may follow inadequate eradication of DCIS.

Side effects of tamoxifen are well defined and generally not serious. Overall among the 900 women allocated to tamoxifen in the preceding trial there were one extra pulmonary embolism, 7 extra deep-venous thromboses, 5 extra endometrial cancers, and no extra deaths. Counterbalancing, there were 29 fewer invasive BCs, and 17 fewer DCISs.

Lancet June 12, 1999; 353: 1986-87 Editorial by Nicholas R C Wilcken, Westmead Hospital, Sydney, Australia.

==========

6-12 TRANS FATTY ACIDS AND CORONARY HEART DISEASE

Trans fatty acids are configured in a straight line. They are solid at room temperature. Cis fatty acids are bent and are liquid at room temperature. Trans fats are more resistant to oxidation and less likely to become rancid with storage or when exposed to the high temperatures used in deep fat frying.

Partial hydrogenation, the process used to create trans acids, removes essential polyunsaturated acids (linolenic; linoleic).

Saturated fats and trans fats are associated with higher LDL-cholesterol levels (adverse effect).

They differ in that trans fats also lower HDL-cholesterol (adverse effect) while saturated fats do not (neutral effect). As a result the LDL-c / HDL-c ratio is significantly higher with a trans fat diet. (Ie, hard margarine produces greater adverse effects than butter.)

The adverse effect of trans fats on the LDL-c / HDL-c ratio is clinically significant. The average intake of 2% of calories as trans fat in the US would be predicted to account for a substantial number of deaths from coronary heart disease (CHD). (2% of a 2000 cal diet = 40 cal = about 4 g fat. One doughnut contains 3.2 g trans fat; one large french fries, 10 g.)

Trans fats also raise triglyceride levels.

A strong correlation exists between intakes of saturated fats and coronary heart disease. The relation between trans fats and CHD is even stronger.

In countries (eg, Spain) where rates of CHD are low, intakes of trans fats are extremely low.

In the US most of the trans fats intakes come from baked goods, fried fast foods, and other prepared foods — considerably more than from home use of stick margarine.

Fats are often lebeled as "cholesterol free vegetable oil". This is misleading.

"These data highlight the need for labeling requirements that include fast foods. Given the proper incentives, the food industry could replace a large portion of the partially hydrogenated fats used in foods and food preparation with unhydrogenated oils." The change would substantially reduce risk of CHD.

NEJM June 24, 1999; 340: 1994-98 Commentary "Sounding Board", first author Alberto Ascherio, Harvard School of Public Health, Boston Mass.

Comment:

Trans fats, of all fats, carry the most adverse effect on lipids.

Monounsaturated fatty acids (eg, olive oil), compared to saturated fatty acids, lower LDL-c without lowering HDL-c. The resultant LDL-c/HDL-c ratio is more favorable. RTJ

==========

6-13 EFFECTS OF DIFFERENT FORMS OF DIETARY HYDROGENATED FATS ON SERUM LIPOPROTEIN CHOLESTEROL LEVELS

Hydrogenation of unsaturated fats forms trans fat and saturates some double bonds. Trans fatty acids have at least one double bond in the trans configuration.

Hydrogenating unsaturated fatty acids (eg, vegetable fatty acids) makes them more plastic and spreadable and more suitable for baking.

Metabolic studies suggest that trans fats have a detrimental effect on serum lipoprotein cholesterol levels as compared with unsaturated fatty acids containing double bonds only in the cis configuration.

This study compared effects on serum lipids of 6 diets containing differing amounts of hydrogenated fat.

Conclusion: Diets high in trans fats and saturated fats had detrimental effects.

STUDY

1. Thirty six healthy subjects (mean age 63) consumed each of 6 diets in random order. Each diet was consumed for 35 days.

2. The foods were identical in each diet which provided 30% of calories from fat. The different fats provided 2/3 of the total fat intake as:

	Grams per 100 g fat					
	Soy bean oil	Semiliquid margarine	Soft margarine	Shortening	Stick margarine	Butter
Saturated fatty acids	13	16	18	17	17	62
Monounsaturated	30	23	26	37	31	24
Polyunsaturated	56	59	45	31	25	4
Trans	0.3	0.6	9	14	26	3

(See correction NEJM September 9, p 856)

RESULTS

	LDL-cholesterol	HDL-cholesterol
1. Butter diet (mean)	177 mg/dL	45 mg/dL
2. Changes compared with butter:		
A. Soybean oil	- 12%	-3%
B. Semiliquid margarine	- 11%	-4%
C. Soft margarine	- 9%	-4%
D. Shortening	-7%	-4%
E. Stick margarine	-5%	-6%

3. Ratios of LDL-cholesterol to HDL-cholesterol were lowest after soybean oil and semiliquid margarine (most beneficial) highest after stick margarine (least beneficial).

DISCUSSION

1. The American Heart Association has suggested substituting unhydrogenated oil for hydrogenated and saturated fat in processed foods and substituting softer for harder margarines and cooking fats.

2. Soybean oil and semiliquid margarine have the lowest levels of trans fats. They are also low in saturated fats. This emphasizes the use of vegetable oils in their natural state.

3. Trans fats were associated with lowering of HDL-cholesterol (adverse effect).

CONCLUSION

The consumption of products low in trans fats and saturated fat has beneficial effects on serum lipoprotein cholesterol levels.

NEJM June 24, 1999; 340: 40 Original investigation, first author Alice H Lichtenstein, Tufts University, Boston Mass.

Comment:

```
            H H H H H  H H
CIS       HC-C-C-C-C=C-C-  (configuration— H on the same side of the double bond )   BENT;  LIQUID
            H H H H        H

              H H H H H    H
TRANS     HC-C-C-C-C=C-C-  (configuration — H on opposite sides of the double bond)  STRAIGHT LINE; SOLID
            H H H H      H H
```

Note that all above fats were associated with a drop in HDL-c compared with butter fat. This makes the LDL-c/HDL-c ratio less favorable. RTJ

6-14 GLUCOCORTICOID THERAPY FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Chronic obstructive pulmonary disease (COPD) refers to a group of disorders characterized by a persistent reduction in the maximal rate of exhalation despite aggressive treatment.

Asthma also causes COPD; severe irreversible airflow obstruction is found in some patients with a long history of asthma and no other identifiable risk factors.

Some patients with COPD have features suggestive of asthma and an acute response to glucocorticoids. But, no study has identified reliable predictors of response. Thus, a therapeutic test may be recommended (3 weeks of prednisone) to assess reversibility.

Both COPD and asthma are thought to be the consequences of chronic airways inflammation, but the nature of the inflammation is quite different:

A. In asthma inflammation is associated with infiltration of eosinophiles, mast cells, and lymphocytes especially helper CD4 T cells). (Glucocorticoids profoundly inhibit production of cytokines by helper T cells.)

B. In COPD, the inflammation is predominantly neutrophilic. Interleukin 8, a potent neutrophilic chemoattractant is strikingly increased.

These differences likely account for the differences in response to treatment in the 2 diseases.

Two studies concerning COPD in the issue of NEJM1,2 reported slight to moderate transient improvement in lung function with oral and inhaled corticoids.

At times patients with acute exacerbations of COPD will have increased numbers of eosinophiles in bronchial biopsy specimens. This may be caused by a respiratory virus infection which attracts eosinophiles and results in a more favorable response to corticosteroids.

NEJM June 24, 1999; 340: 1990-91 Editorial by Homer A Boushey, University of California, San Francisco.

1. "Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease" NEJM June 24, 1999; 340: 1941-47
2. "Long-term Treatment with Inhaled Budesonide in Persons with Mild Chronic Obstructive Pulmonary Disease who Continue Smoking' NEJM June 24, 1999; 340; 1949-53

==========

6-15 EFFECT OF CIGAR SMOKING ON THE RISK OF CARDIOVASCULAR DISEASE, CHRONIC OBSTRUCTIVE PULMONARY DISEASE, AND CANCER IN MEN.

The upward trend of cigar smoking is mainly by young and middle-aged men of relatively high socio-economic status. Cigars are generally perceived as safer than cigarettes. The association between cigar smoking and cardiovascular disease, COPD, and cancer has not been clearly established.

This cohort study assessed whether cigar smoking is related to increased risk.

Conclusion: Cigar smoking independently increased risk of all the above.

STUDY

1. Cohort study followed almost 18 000 men age 30 to 85 at baseline.
2. None reported having smoked cigarettes. None were currently smoking a pipe.
3. About 9% smoked cigars; 91% did not. Most cigar smokers smoked fewer than 5 cigars daily.
4. Followed for up to 24 years for incidence of coronary heart disease (CHD), COPD, upper-aero-digestive cancer, and cancer of the lung

RESULTS

1. Compared with non-smokers, cigar smokers were at higher risk of CHD (RR = 1.3); COPD (RR = 1.5); upper aero-digestive cancer (RR = 2); cancer of lung (RR = 2.1). There was a dose-related response — increased risks were mainly in those who smoked 5 or more cigars daily.
2. On average, cigar smokers were slightly older, had a higher body mass index, higher blood pressures, higher cholesterols, and were more likely to have diabetes.
3. There appeared to be a synergistic relation between cigar smoking and alcohol consumption and risk of cancers of the upper aero-digestive tract.
4. The majority of cigar smokers continued to smoke cigars over 8 years.
5. Interestingly, fewer than 4% switched to cigarettes.

DISCUSSION

1. In this cohort study of male health-plan enrollees, cigar smoking was associated with a moderate but significant increase in risk of CHD, COPD, and cancers of the lung and upper aero-digestive tract.
2. Increased risks were mainly seen among those who smoked 5 or more cigars daily as compared with non-smokers.
3. Risks were much lower than for current cigarette smokers whose typical relative risks of the above diseases are 2 to 12 times greater than for cigar smokers.
4. Cigar smoke contains the same toxic and carcinogenic compounds found in cigarette smoke. Smoking 4 or more cigars daily is in this regard equivalent to smoking 10 cigarettes.

CONCLUSION

Independent of other risk factors, regular cigar smoking can increase risk of coronary heart disease, COPD, and cancers of the lung and upper aero-digestive tract.

NEJM June 10, 1999, 340: 1773-80 Original investigation, first author Carlos Iribarren, Kaiser Permanente Medical Care Program, Oakland CA

Comment:

Some have suggested that among smokers who refuse to quit, substituting cigars for cigarettes may be less risky. If cessation is impossible, why not substitute cigars? The lessened risk comes primarily from reduced quantity of smoke, especially inhaled smoke.

Certainly, cigars are not safe, but clinical medicine often compromises, choosing an intervention yielding a lower risk if complete elimination of the risk is impossible.

Clinicians may be cautious about advising cigars in place of cigarettes for medical-legal reasons. Explicit cautions should be documented.

The U. S. Surgeon General comments in an editorial in this issue (pp 1829-31): "It is critical that cigars not be construed as a safe or less costly alternative to cigarettes." RTJ

==========

REFERENCE ARTICLE

6-16 RECENT ADVANCES IN VARICELLA-ZOSTER VIRUS INFECTION

Varicella-Zoster virus (VZV) remains latent in the body throughout life. It reactivates in 15% of persons, causing herpes zoster (shingles).

This article addresses molecular biology and immunology of the VZV; transmission; clinical features; and diagnosis; management of varicella, zoster, and postherpetic neuralgia; and prevention of varicella and zoster.

The article presents a table of therapy for both varicella and zoster in both immouncompetent and immunocompromised patients. (p 927)

VZV infections (chicken pox) are much more severe in immunocompromised individuals. These patients are more likely to have disseminated disease. (Eg. children with HIV infection.) Intravenous acyclovir [Zovirax] is required for treatment of serious infections. Systemic corticosteroid therapy increases morbidity in patients with chicken pox even in those without other immunocompromising conditions, especially when administered during the incubation period of varicella. Even small doses may place patients at risk for severe varicella. Inhaled beclomethasone may also be associated with severe varicella.1.

The recently licensed live attenuated vaccine for VZV is effective in preventing chicken-pox. A substantial risk is associated with the live vaccine in immunocompromised persons. These patients should not be vaccinated except as part of clinical trials. Pregnant women should not receive the vaccine because of the theoretical risk for fetal varicella.

For patients with zoster, adding steroids to acyclovir speeds the resolution of acute pain and the return to normal daily activities. This justifies use in persons older than 50 who have no relative contraindications (diabetes, hypertension, glaucoma). The vaccine's ability to stimulate immunity in adults suggests a promising strategy to modify the course of herpes zoster. The observation that most persons develop zoster only once, if at all, suggests that one episode of zoster may enhance immune responses to levels that are sufficient to prevent recurrences.

After postherpetic neuralgia is established it is difficult to treat. The only licensed treatment is a topical ointment containing extract of chili peppers (Capsaicin). Low dose tricyclic antidepressants (eg amitriptyline [Elavil — 25 mg daily) relieves the neuropathic pain process. Gabapentin [Neurontin] (an anticonvulsant), added to the existing regimen may provide substantial alleviation of pain. Carbamazepine [Tegretol] alleviates lancinating pain; topical lidocaine provides transient local relief. Other modalities which may be tried include regional nerve blocks, transcutaneous electrical stimulation, and acupuncture. "Narcotics can be beneficial and are generally underused."

Annals Int. Med. June 1, 1999; 130: 922-32 NIH conference, moderator Jeffrey I Cohen, National Institute of Allergy and Infectious Diseases, Bethesda, MD.

Comment:

1. This is an apparent contradiction since corticosteroids have been recommended early in the course of zoster. There must be a difference in the pathogenesis relative to immunity.

There is evidence that administration of small daily doses of amitriptyline early in the course of zoster may lower incidence and severity of postherpetic neuralgia. RTJ

6-17 REHABILITATION OF HEMIPARESIS AFTER STROKE WITH A MIRROR

In patients with immobile phantom limbs after amputation, vivid kinaesthetic sensations of movement can be evoked when the patient watches movement of the non-amputated hand or arm in a vertical parasaggital mirror.

This study conducted mirror therapy on patients with hemiparesis following stroke.

Entered 9 patients, at least 6 months post-stroke, randomly assigned to 4 weeks using a mirror (see illustration) or transparent plastic. Then crossed over for the next 4 weeks. Practice periods were conducted for 15 minutes twice daily. Patients moved both hands or arms symmetrically (moving the affected arm as best they could) while watching the good arm in the mirror, or the paretic arm through the plastic.

The regimen asked patients to move the affected limb proximal to distal, working from movements they could perform to those they could not perform.

Subjectively, all patients felt the mirror was more helpful than the plastic. One commented that the mirror seemed to exercise his brain and nerves as well as muscles. One liked using the mirror because it looked like the bad arm was moving normally.

Two blinded senior neurologists found more patients improved on the mirror.

The mirror provides a "proper" visual input. The mirror reflection of the moving good arm looks like the affected arm is moving correctly – and perhaps substitutes for the often decreased or absent propriceptive input. Use of the mirror may help recruit the premotor cortex to help with motor rehabilitation. The premotor cortex has a number of features suggesting it might be a link from the visual image in the mirror to motor rehabilitation; may contribute to the descending corticospinal tracts; and provide some bilateral control of movement. "On a number of neurological and psychological levels, mirror therapy may help to reverse elements of learned disuse of the affected limb."

Lancet June 12, 1999; 2053-54 "Research Letter", first author Eric L Altschuler, University of California, San Diego.

Comment:

I would be interested to ask our local physiotherapists if they have any experience with this modality. RTJ

==========

REFERENCE ARTICLE

6-18 STANDING STATISTICS RIGHT SIDE UP

This editorial comments on two articles addressing medical statistics.1, 2 The articles are tough reading. I believe readers, to fully understand, must have a greater grounding in statistics than I have. Nevertheless, I did gain some insight into the limitations of the "P value" and application of the Bayes factor. RTJ

What clinicians and patients really need is a way to calculate the probability that any particular test result, positive or negative, is a true result. Doing so requires combining sensitivity and specificity to create something called a likelihood ratio, which is an overall measure of the "evidence" provided by the test result (positive or negative) itself. The likelihood ratio3 is then used to modify the pretest estimate (the prior probability) that the patient has the disease, thereby creating a new and better post-test estimate —the posterior probability that the patient has the disease, given the positive test.

Bayes theorem is essentially a quantitative description of what we do, qualitatively, every minute of the day: use new information inductively to refine our judgements about the correctness of what we already know. Baysian inference says that the most effective way to develop a new and better degree of confidence (posterior probability) in our knowledge is to combine our previous confidence, derived from sources outside a particular test or study (prior possibility) with the "evidence" from that test (the likelihood ratio of the test — the Bayes factor).

Figuring the best way to assess the prior possibility of a disease based on information from

sources outside the trial is an important challenge. It is also a very difficult one, because we often weigh outside information subjectively.

The editorialist comments — "In our view, the articles will contribute importantly to the task of standing statistical inference right side up, We recommend it to our readers' most serious attention"

Annals Int. Med. June 15, 1999; 130: 1019-21 Editorial by Frank Davidoff, Editor The Annals Internal Medicine, American College of Physicians, Philadelphia, PA

1. "Toward Evidence-based Medical Statistics. 1: The P value Fallacy" Annals Int. Med. June 15, 1999; 130: 995-1004 Steven N Goodman, Johns Hopkins University School of Medicine, Baltimore, MD

2. "Toward Evidence-based Medical Statistics. 2: The Bayes Factor" Annals Int. Med. June 15, 1999; 130: 1005-13 Steven N Goodman, Johns Hopkins University School of Medicine, Baltimore, MD

Comment:

3. The likelihood ratio of a positive diagnostic test result for the disease in question is simply the number of true positive test results (expressed as a %) divided by the number of false positive test results (expressed as a %). (Sensitivity of the test divided by 1 minus the specificity of the test) RTJ

==========

6-19 OPTIMISATION OF ANTIHYPERTENSIVE TREATMENT BY CROSSOVER ROTATIONS OF FOUR MAJOR CLASSES

Most studies of antihypertensive agents in unselected patients with essential hypertension emphasize the similarity of average response to the different drug groups, despite widely differing mechanisms of action. However, essential hypertension is a heterogeneous disorder. It would be surprising if the variable pathogenesis did not cause detectable variability in individual responses to different agents.

This is a study of young hypertensives. It asked whether and by how much a systematic rotation of patients through 4 drug classes would provide better therapy.

Conclusion: There was a marked variability in response to different drugs. Optimization of therapy required systematic rotation of 4 drugs.

STUDY

1. Open-label 4-way crossover study entered 56 patients (age 22 to 51; all white). Mean BP = 161/98. None had been previously treated with antihypertensive drugs.

2. Drugs were cycled for 7 months, if necessary to achieve a BP ≤ 135/85.1

3. Cycles lasted 1 month followed by 1 month washout: ACE inhibitor (lisinopril) 20 mg; beta-blocker (bisoprolol) 5 mg; diuretic (hydrochlorothiazide-triamterine) 25 mg + 50 mg; and calcium blocker (nifedipine) 30 mg. The starting drug was randomized.

4. If the BP was over 135/85 on the best drug, the patient was titrated up to a dose twice the standard dose. If the single best drug was still ineffective, a second drug was added. (The second drug was chosen by a AB/CD rule (ACE-Beta/Calcium-Diuretic). Ie, if the best first drug was A or B, then C or D was added as a second drug. This because these classes are generally considered to have complementary and additive effects.

5. Repeated the most effective drug on completion of the rotation to confirm its efficacy.

RESULTS

1. Significant variability in response was found.

2. Only 20% achieved ≤ 135/85 on the first drug tried. Rotation increased the number achieving ≤ 135/85 up to 50%.1

3. Fifty patients remained in the study. All 50 achieved BP ≤ 135/85:

A. 23 (46%) achieved a BP ≤ 135/85 on a single drug with acceptable tolerability. (I could not determine from the text how many required doubling the dose. RTJ)

B. 21 (42%) achieved a BP ≤ 135/85 on a combination of one drug from AB and one from CD

C. 6 required a third drug or addition of an alpha-blocker.

4. Responses to the AB pair were at least 50% higher (more effective) than the CD pair.

5. Best responses: ACE inhibitor—16; Beta-blocker – 10; Calcium blocker – 4; Diuretic – 4.

6. 49 patients had their BP rechecked at 1 year. Only 2 required readjustment of therapy.

DISCUSSION

1. Many patients who responded poorly to one drug responded well to another.

2. "We found significant variability in the response of most patients to the four main classes of antihypertensive agents. This variability was such that only a minority of patients were likely to receive their best drug first, or to reach a conventional target for blood pressure treatment without the process of systematic rotation."

3. The results are at variance with most current guidelines which point to a stepped-care approach when there is no fall in BP after the first drug is started.

4. "The practical implications of our findings are considerable. In our study of over 6000 hypertensive patients treated in general practice, we found that 31% of patients were receiving at least two drugs despite which only 35% of patients had a blood pressure of 140/90 or less.

5. By contrast, the rotation strategy resulted in almost twice as many patients being controlled on a single drug.

6. The doses were generally considered submaximal. The study aimed to maximize tolerability.

7. Provisionally, the authors recommend that patients younger than 50 start on one of the AB pair and switch to one of the CD pair if needed. Patients over 60 would proceed on the reverse order. This would forestall in some patients the need to assess the best of C or D, or the best of A or B.

8. This offers support for the expectation of distinct syndromes within the umbrella of essential hypertension.

CONCLUSION

There is a marked variability in hypertensive patients' response to different antihypertensive drugs. Optimization of treatment requires systematic rotation through several therapies. An AB/CD rule is proposed in which one of each of the two pairs is initially selected to abbreviate the rotation in routine practice. (Ie, if one of A or B does not achieve target, go to one of C or D.)

Lancet June 12, 1999; 353: 2008-13 Original investigation, first author J E Claire Dickinson, University of Cambridge, UK

Comment:

1. The study also assessed results based on a target of 140/90. Rotation with the aim of selecting only one drug was more successful in this group. "With 140/90 mmHg as the target for blood pressure reduction, our findings suggest that monotherapy can be the aim in all but a few patients."

Note that this was a study of relatively young patients with hypertension. Results cannot be extrapolated to older patients.

This continues the debate about: 1) single drug therapy for hypertension (at times at higher dosage) vs 2) multiple drug therapy at lower dosage. I believe most authorities choose 2). Adverse effects of drugs usually depend on dose. Using multiple drugs at lower dosage results in fewer adverse effects while their effects are additive.

I believe also that the regimen is too complex for routine use in primary care practice.

The point about choosing a first drug from AB and an added drug from CD is notable. This would include a combination of diuretic + beta-blocker, still a standard recommendation.

I found the article difficult to abstract. I hope I accurately reported the main results. RTJ

==========

REFERENCE ARTICLE

6-20 LABORATORY DIAGNOSIS OF VITAMIN B12 AND FOLATE DEFICIENCY

A Guide for the Primary Care Physician

"At one time the diagnosis of a deficiency of vitamin B12 or folate was considered to be relatively straightforward. As knowledge has accumulated, the limitations of such tests as serum vitamin level measurements and the Schilling test have become apparent."

With the development of newer tests, atypical and subclinical deficiency states have been recognized. This article reviews available tests used in the diagnosis. It presents a rational approach to the diagnosis. (See table 1 p 1290 for excellent reviews of cobalamin and folate absorption and transport.)

"The accurate diagnosis of (deficiencies) is a complex task. No easily performed test can reliably serve as a diagnostic gold standard."

Archives Int Med., June 28, 1999; 159: 1289-98 Review article by Christopher F Snow, Santa Clara Valley Medical Center, San Jose, CA.