PRACTICAL POINTERS
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MARCH 2000

IMPORTANCE OF TREATING ISOLATED SYSTOLIC BLOOD PRESSURE

BETA-BLOCKERS IMPROVE HEART FAILURE PATIENT'S QUALITY-OF LIFE

WATCH OUT! NSAIDs CAN WORSEN HEART FAILURE

STEROLS AND STANOLS ADDED TO MARGARINES REDUCE LDL-CHOLESTEROL

EMPATHIC PHYSICIANS CAN EASE BURDENS OF TERMINAL ILLNESS

AIM FOR A LONG HEALTHY LIFE, AND ACCEPT A NATURAL PEACEFUL DEATH

BENEFITS OF MEDICAL TERMINATION OF PREGNANCY

GUIDELINES FOR USE OF ANTICOAGULATION IN ATRIAL FIBRILLATION

LIKELIHOOD RATIOS — UNDERSTANDING INCREASES FUN OF READING

CIGARETTE SMOKING AND RISK OF INVASIVE PNEUMOCOCCAL DISEASE

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YOU LIKELY GAIN WEIGHT DURING THE HOLIDAYS AND DON'T LOSE IT

TUMOR NECROSIS FACTOR TO TREAT RHEUMATOID ARTHRITIS

CARDIOVASCULAR DISEASE RISK — MULTIPLE RISK FACTORS PREDICT IT

GLUCOSAMINE AND CHONDROITIN TO TREAT OSTEOARTHRITIS

AMIODARONE TO PREVENT RECURRENCE OF ATRIAL FIBRILLATION

RECOMMENDED READING

REFERENCE ARTICLES

JAMA, NEJM, LANCET
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HIGHLIGHTS MARCH 2000

3-1 RISKS OF UNTREATED ISOLATED SYSTOLIC HYPERTENSION IN THE ELDERLY

A recent sea change. Understanding the risks of isolated systolic BP (defined arbitrarily as systolic > 160 with diastolic < 95) has changed our approach to treatment. Isolated systolic BP is more predictive of future cardiovascular events than elevated diastolic. Indeed, when combined with a high systolic, a low diastolic (with the associated increase in pulse pressure) *increases* risk.

Drug treatment of systolic BP over 160 in older individuals effectively reduces risk and is indicated regardless of diastolic BP.

Primary care physicians have the responsibility of recognizing and opportunity of treating isolated systolic BP in their elderly patients.

3-2 EFFECTS OF CONTROLLED-RELEASE METOPROLOL ON TOTAL MORTALITY, HOSPITALIZATIONS, AND WELL-BEING IN PATIENTS WITH HEART FAILURE (MERIT-HF)

3-3 BETA-BLOCKER THERAPY FOR HEART FAILURE

An important addition to understanding benefits of beta-blockers in treatment of mild or moderate heart failure. Metoprolol was associated with reduction in cardiovascular events and also improvement in quality of life and functional class.

Use of beta-blockers in treatment of heart failure has become a dominant part of standard therapy. (Another sea change.) Primary care physicians should be among those who prescribe them most often.

But, start low and go slow.

3-4 CONSUMPTION OF NSAIDs AND THE DEVELOPMENT OF CONGESTIVE HEART FAILURE IN ELDERLY PATIENTS.

Primary care clinicians should be mindful of, and responsive to, the important adverse effects of NSAIDs (including the new COX-2 inhibitors). Adverse effects on the GI tract, blood pressure, and renal function as well as cardiac function are a nationwide problem due to widespread use.

3-5 PLANT STEROL AND STANOL MARGARINES AND HEALTH

These sterols, added to margarines and other fat foods, inhibit absorption of both dietary and biliary cholesterol, resulting in significant lowering of LDL-cholesterol. They can be an important addition to lipid control in select patients who enjoy the taste, can afford the cost, and use them regularly. They are non-toxic.

3-6 UNDERSTANDING ECONOMIC AND OTHER BURDENS OF TERMINAL ILLNESS: The Experience of Patients and Their Caregivers.

Primary care clinicians must be ever mindful of, and respond to, the emotional and financial stress patients, caregivers, and families undergo when facing a terminal illness. An empathetic physician can relieve some of the burdens.

3-7 DEATH AND THE RESEARCH IMPERATIVE

A prominent ethicist promotes the idea that, since death is a normal part of life, we should not compulsively use technology to maintain life when palliative care would be more appropriate. Death is not the principal evil of human life. We should not fight death to the end. Research should focus on premature death; should aim to shorten the period of poor health, pain, and impairment before death. Clinicians should help patients achieve a peaceful death. Preservation of life is not always a higher ideal than a peaceful death. Medical progress should be redefined as prevention of illness and disability — and a reduction in conditions that do not cause death, but ruin lives. It is not death that people seem to fear the most, but a life poorly lived.

3-8 MEDICAL TERMINATION OF PREGNANCY

A safe method of terminating early pregnancy medically is available. Making it available would save thousands of lives yearly. “Legalization of abortion has not been associated with increase in demand for abortion.”

3-9 DECISION ANALYSIS AND GUIDELINE FOR ANTICOAGULANT THERAPY TO PREVENT STROKE IN PATIENTS WITH ATRIAL FIBRILLATION

Although the majority of patients with atrial fibrillation will benefit from anticoagulation to prevent embolic stroke, some patients will not benefit. This decision analysis is based on age, systolic BP, presence of cardiovascular disease, and left ventricular hypertrophy. It presents tables indicating clear benefit, or no benefit from anticoagulation in 12 categories of risk. Patient preference is basic to the decision to use anticoagulation.

3-10 LIKELIHOOD RATIOS

The second step in the analysis of the value of diagnostic tests. Understanding increases the enjoyment of reading the journals.

3-11 CIGARETTE SMOKING AND INVASIVE PNEUMOCOCCAL DISEASE

3-12 SMOKING AND PNEUMOCOCCAL DISEASE

In immunocompetent individuals, smoking is a strong, independent risk factor for invasive pneumococcal disease. “It may be reasonable to incorporate pneumococcal vaccine into smoking cessation programs as well

as to consider vaccinating those who continue to smoke."(Immuno-incompetent individuals [eg, HIV-infected] are also at high risk.)

3-13 CHANGING CARRIAGE RATE of *NEISSERIA MENINGITIDIS* AMONG UNIVERSITY STUDENTS DURING THE FIRST WEEK OF TERM

Carriage rates of meningococci among university students increases rapidly during the first week of the term, and increases further during the term. Your college student child should avoid smoking, crowding, and intimacy as much as possible. A case can be made for immunization. We should be alert to the possibility of invasive disease when a healthy student becomes suddenly and seriously ill, and be prepared to administer intramuscular penicillin based on clinical suspicion, without waiting for diagnostic confirmation.

3-14 A PROSPECTIVE STUDY OF HOLIDAY WEIGHT GAIN

The weight gain during the holiday season averages about a pound. The problem is — we do not lose the pound during the rest of the year. Weight gradually increases over the years. If we do not wish to avoid holiday food and cheer, we should make a conscious effort to increase activity during the season.

3-15 TUMOR NECROSIS FACTOR BLOCKERS IN RHEUMATOID ARTHRITIS

"For patients with rheumatoid arthritis, a new era of treatment has begun." Primary care clinicians stay alert for developments.

3-16 THERAPEUTIC MONOCLONAL ANTIBODIES

These agents are being investigated as therapeutic agents for rheumatoid arthritis, Crohn's disease, anti-platelet activity, and antiviral activity. Application may be widespread. Primary care clinicians stay alert for developments.

3-17 GUIDELINES ON PREVENTING CARDIOVASCULAR DISEASE IN CLINICAL PRACTICE.

3-18 ESTIMATING CARDIOVASCULAR RISK FOR PRIMARY PREVENTION: Outstanding Questions For Primary Care

Primary care clinicians should keep one of the tables now available to inform patients of their risk of developing cardiovascular disease within the next 10 years. Absolute risk is strongly influenced by a combination of risk factors. Drug therapy (especially for lipid and BP control) should be considered for those at high risk. A 30% risk over 10 years identifies over 3% of the population. This is in addition to the 5% with established disease who also require drug therapy.

3-19 GLUCOSAMINE AND CHONDROITIN FOR TREATING SYMPTOMS OF OSTEOARTHRITIS

The mechanism of action is not known, purity of compounds available not established, and toxicity not defined. The authors conclude, nevertheless, that there may be some benefit in symptomatic management. Primary care physicians should not prescribe them. But, what to do when a patient who is taking them reports benefit?

3-20 AMIODARONE TO PREVENT RECURRENCE OF ATRIAL FIBRILLATION.

Evidence that, in low dose, it is more effective than other anti-arrhythmics in preventing recurrence of atrial fibrillation. Amiodarone is a "difficult" drug. It is best left to cardiologists or others experienced with use to prescribe and follow.

3-21 NEW GUIDELINES FOR STROKE PUBLISHED

Aspirin and stroke units are effective therapy. Thrombolysis should be reserved for specialized centers.

3-22 SCABIES AND PEDICULOSIS

A review. Permethrin and lindane are reasonable choices for local application.

3-23 NON-INVASIVE METHODS OF ARTERIAL AND VENOUS ASSESSMENT

A review.

3-24 NEUROLOGICAL COMPLICATIONS OF THE REACTIVATION OF VARICELLA-ZOSTER VIRUS

A review of unusual CNS complications. Aggressive therapy beginning as soon as possible after onset of herpes zoster may reduce severity of post-herpetic neuralgia. Treatment of established post-herpetic neuralgia is still unsatisfactory. Opiates are underused to help control pain.

3-25 RECOMMENDED READING

3-7 DEATH AND THE RESEARCH IMPERATIVE

3-27 REFERENCE ARTICLES

3-8 MEDICAL TERMINATION OF PREGNANCY

3-9 DECISION ANALYSIS AND GUIDELINE FOR ANTICOAGULANT THERAPY TO PREVENT STROKE IN PATIENTS WITH ATRIAL FIBRILLATION

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3-17 GUIDELINES ON PREVENTING CARDIOVASCULAR DISEASE IN CLINICAL PRACTICE.
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3-22 SCABIES AND PEDICULOSIS
3-23 NON-INVASIVE METHODS OF ARTERIAL AND VENOUS ASSESSMENT
3-24 NEUROLOGICAL COMPLICATIONS OF THE REACTIVATION OF VARICELLA-ZOSTER VIRUS

3-1 RISKS OF UNTREATED ISOLATED SYSTOLIC HYPERTENSION IN THE ELDERLY

Prevalence of isolated systolic hypertension (**ISH**) rises curvilinearly with age and exceeds 25% in those over age 80. It is a distinct pathophysiological entity in which the rise in systolic BP is due mainly to decreased elasticity of the large arteries. It is not necessarily accompanied by a rise in mean arterial pressure or in peripheral resistance.

Among the cardiovascular risk factors amenable to prevention in the elderly, ISH is of major importance. Three outcome trials have specifically addressed the question whether in the elderly the cardiovascular risk conferred by ISH is reversible by antihypertensive drug treatment. (*See references 2-4*)

This study reanalyzed evidence from published trials regarding ISH. It evaluated the risk conferred by systolic and diastolic pressures at baseline, then calculated estimates of relative and absolute benefit from antihypertensive drug treatment. Previous meta-analyses have not specifically focused on ISH and have explained drug treatment benefit mainly as related to achieved diastolic BP

Conclusion: Drug treatment is justified in older patients with ISH 160 or higher.

STUDY

1. Meta-analysis considered 8 trials (over 15 000 patients) of patients age 60 and over (the majority female).

All had systolic ≥ 160 and diastolic < 95. Compared treated patients with untreated patients.

2. Various antihypertensive drugs were used. In general, to reach the target BP, a stepped-care approach was used. The dose of the first line medication was increased and second- and third-line drugs introduced. (Combinations of thiazide, calcium-blocker, ACE inhibitor, or beta-blocker.)
3. The target systolic BP was below 160 or below 150, or a decrease of at least 20 to 30 mm Hg from baseline.
4. Outcomes — total and cardiovascular mortality, all cardiovascular complications, fatal and non-fatal stroke (not TIA), and fatal and non-fatal coronary events.
5. Applied statistical methods to model the risks associated with BP. [1]
6. Median follow-up = 4 years.

RESULTS

1. BP averaged 174/83 at baseline.
2. Total mortality was positively correlated with systolic BP at entry. After correction for age, sex, and diastolic BP, the relative hazard rates associated with 10 mg higher initial systolic BP were 1.26 for total mortality, 1.22 for stroke, but only 1.07 for coronary events. (*See figure 1 p 867 for risk of death at various BP levels in control patients. At a mean age of 70, a systolic of 200 with a diastolic of 70 was associated with an increased risk of death in about 30 patients per 100 over 2 years.)*
2. Independent of systolic BP, diastolic BP was *inversely* correlated with mortality. (Ie, the *lower* the diastolic, the greater the mortality.) This highlights the role of pulse pressure as a risk factor.
3. Benefits of treatment:
   A. Active treatment was associated with a mean decrease in BP of 10/4 mm Hg. The net reductions expressed as a percentage of baseline averaged 6% systolic and 5% diastolic.
   B. Across all trials, active treatment reduced total mortality by 13%; cardiovascular deaths by 18%.
   C. The pooled reduction in fatal combined with non-fatal events was 26% for all cardiovascular complications; 30% for stroke; and 23% for coronary events.
   D. Absolute benefit of active treatment was particularly effective in men, older patients, and patients with previous cardiovascular complications.
4. To prevent one major fatal or non-fatal cardiovascular event, over 5 years the number needed to treat: men = 18; women = 38; age 60-69 = 39; with previous cardiovascular complications = 16; without previous cardiovascular complications = 37.
5. If pulse pressure at baseline was 90 mm Hg or more, NNT to prevent one cardiovascular death = 63. For pulse pressure under 90, the NNT was 119. (Ie, treatment was more effective as pulse pressure increased.)

DISCUSSION

1. Previous meta-analyses focused on role of diastolic BP as a risk factor and studied the benefit of drug treatment relative to the reduction in diastolic BP.
2. This study found that systolic BP in untreated patients with elevated systolic BP was a more accurate predictor of mortality and cardiovascular complications than their diastolic BP. Increases in systolic of 10 mm Hg were significantly and independently correlated with increases of nearly 10% in fatal and non-fatal complications (except for coronary events).
3. Diastolic BP was *inversely* correlated with risk. "At any level of systolic blood pressure, the risk of death rose with lower diastolic blood pressure, and therefore with greater pulse pressure." (Systolic minus diastolic).
4. These findings may have important clinical applications. "The target level of blood pressure to be reached by antihypertensive drug treatment should, in older patients, be based on systolic rather than diastolic blood pressure."
5. "In our analysis, active treatment reduced both systolic and diastolic pressure by 5%. Because systolic blood pressure at entry was a positive risk factor, whereas diastolic was not, one may assume that the benefit of treatment was overwhelmingly due to the reduction of systolic blood pressure."

CONCLUSION

Drug treatment is justified in older patients whose systolic BP is 160 or higher regardless of diastolic BP. Absolute benefit was greater in men, in older patients, in those with established cardiovascular disease, and those with greater pulse pressure. In relative and absolute terms, treatment prevented stroke more than coronary events.

Lancet March 11; 2000: 355: 865-72 Original investigation, first author Jan A Staessen, University of Leuven, Belgium

Comment:

1 See text for methods used. I do not understand all the statistical terms and methods the authors applied to their analysis, but I do not believe clinicians are required to fully understand details of statistics to gain clinical meaning from the study.

The emphasis on systolic BP and pulse pressure (rather than diastolic) is gaining strength in current studies. This is a sea change from previous teaching which older clinicians will recognize as turning their clinical world upside down. I believe the concept is more clinically important than the sea change brought about by the discovery of the link between *H pylori* and peptic ulcer.

Question: Since pulse pressure is a major risk factor, will reducing it by increasing diastolic BP benefit? I doubt it because this intervention would not affect the basis for the increase in pulse pressure,

which is loss of elasticity of the great vessels leading to an increase in systolic pressure. Lowering systolic is the key intervention. RTJ

3-2 EFFECTS OF CONTROLLED-RELEASE METOPROLOL ON TOTAL MORTALITY, HOSPITALIZATIONS, AND WELL-BEING IN PATIENTS WITH HEART FAILURE (MERIT-HF)

Angiotensin -converting enzyme (**ACE**) inhibitors have been established as beneficial therapy for patients with chronic heart failure (**HF**) due to left ventricular systolic dysfunction. But, mortality still remains high.

Recent studies of the effects of beta-blockade in patients with HF also demonstrate a reduction in mortality. However, their effect on frequency of hospitalizations, symptoms, and quality of life has not been fully explored.

This study examined the effects of the beta-1 (cardioselective) blocker metoprolol on mortality, hospitalizations, symptoms, and quality of life in patients with *symptomatic* HF.

Conclusion: Metoprolol was associated with improved survival, reduced hospitalizations, and improved function and quality of life.

STUDY

1. Randomized, double-blind, placebo-controlled multicenter trial entered over 3900 patients (mean age 64) with chronic HF. Ischemic etiology — 65%; NYHA class II or III — 96%; mean ejection fraction — 0.28; previous myocardial infarction — 48%; hypertension — 44%; diabetes — 25%.
2. All were stabilized on optimum standard therapy. The great majority were taking a diuretic, an ACE inhibitor, and digitalis. Few were taking spironolactone. These drugs were continued.
3. Randomized to: 1) metoprolol CR/XL (controlled release/extended release) starting at 12.5 to 25 mg daily, or 2) placebo.
4. Dose of metoprolol was gradually increased by doubling the dose every 2 weeks with a target dose of 200 mg daily according to individual tolerance.
5. Follow-up, up to 18 months.

RESULTS

1. The target dose of 200 mg daily was reached by 64% of patients; 87% received 100 mg or more. Mean dosage = 159 mg.

2. After 18 months	Metoprolol	Placebo	NNT(18 months to benefit one)
Total mortality or all-cause hospitalization	32%	38%	16

Total mortality or hospitalization due to worsening HF	16%	22%	16
Death or heart transplantation	7.5%	10.9%	26
Cardiac death or non-fatal myocardial infarction	7%	11.2%	24
Total mortality or hospitalization or ER visit due to HF	16%	23%	14

(*Note: these are my calculations from their reported relative risk reductions – table 2 p 1298. RTJ*)

3. Improvements in NYHA functional class of HF

	Metoprolol	Placebo	Absolute difference
Total improved	28.6%`	25.8%	3.2%
Improved by 1 class	26%	24.3%	1.7%
Improved by 2 classes	2.6%	1.5%	1.1%

(*Note how many in the placebo group actually improved over 18 months. RTJ*)

4. A subset of patients (n = 741) participated in a quality of life evaluation: 36% of metoprolol patients reported important improvements in their overall treatment evaluation scores vs 29% of the placebo patients. Fourteen patients needed to be treated for 18 months for one to report greater improvement in quality of life as compared with placebo.
5. Adverse effects: withdrawals due to worsening HF occurred in 3.9% of metoprolol group vs 5.% in placebo; withdrew for any adverse event. 9.8% of metoprolol group vs 11.7% of placebo group

DISCUSSION

1. Metoprolol CR/XL given once a day in addition to other conventional drugs, improved survival and lessened hospitalization due to worsening HF, reduced the number of days spent in the hospital, and improved symptoms and well-being.
2. The drug was well tolerated. Adverse effects leading to withdrawals were more common in the placebo group.
3. It is safe to treat patients with heart failure with beta-blockers by using a low starting dose and gradually increasing the dose.
4. The study did not present any valid conclusions regarding patients with NYHA class IV heart failure. (Ie, those confined to bed.) The number of patients in this group was small and the effect equivocal.

CONCLUSION

Metoprolol, controlled release/extended release, added to standard therapy for patients with symptomatic heart failure, improved survival, reduced the need for hospitalizations due to worsening heart failure, improved functional class, and had beneficial effects on patient well-being.

JAMA March 8, 2000; 283; 1295-1302 Original investigation by the Metoprolol CR/XL Randomized Intervention Trial in Congestive Failure (MERIT-HF) group, first author Ake Hjalmarson, Sahlgrenska University Hospital, Goteborg, Sweden

Comment:

Drug trials published in the flagship journals persist in reporting relative risk reductions rather than absolute risk reductions and the number needed to treat. To determine the latter, one has to dig the numbers out of the data and recalculate. It is certainly more impressive to report a 35% relative risk reduction in an end point rather than an absolute reduction of 7%. Only absolute changes in risk are meaningful to clinicians and patients. I believe editors will in the future require reporting in absolute terms.

Note that, in the placebo group, many patients improved in functional class as judged by their physicians, and many patients improved in quality of life as judged by themselves. Why? I suspect that it was because the placebo group received additional support and oversight, and likely increased compliance with standard therapy. This is an important message for primary care clinicians.

Despite this therapeutic improvement, the prognosis of HF remains poor. Mortality and hospitalizations continue to rise over 18 months with no apparent let up. I believe the most important benefit of beta-blockers in treatment of HF is the relief of symptoms and improved quality of life.

Heart failure has become a multi-drug and complex therapeutic challenge. RTJ

3-3 BETA-BLOCKER THERAPY FOR HEART FAILURE

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

The study demonstrated that, in this patient population, beta-blocker therapy is close to the dominant therapy category. (Ie, should be used in all eligible patients.) Twenty years ago, beta-blockers were considered contraindicated in HF because they reduce myocardial contractility. It is now known that modulation of beta-receptors has a much more far-reaching impact on the complex mechanisms of myocardial function and vulnerability to risk of sudden death.

However, the effect on the many patients with HF who do not have systolic dysfunction (HF due to diastolic dysfunction — ie, no decrease in ejection fraction) is not known. Likewise, the effect (beneficial or harmful) on patients with class IV HF remains unknown.

Benefit was evident from addition of metoprolol to an already complex drug regimen. “Clinicians must remain humble about the uncertainty regarding interactions, both positive and negative, in such a complex therapeutic environment.”

Previous studies and anecdotal experience demonstrated that when beta-blockers are initiated, quality of life tends to deteriorate (not improve) in the first few days of weeks. Patients are also

concerned about depression and impotence. However, surprisingly little objective data have been generated about these concerns.

Given the overwhelming evidence of benefit of beta-blockers in HF . . ."It would be difficult to make an argument that beta-blockers should be withheld from any patient meeting the general criteria for entry into clinical trials." Yet data indicate that less than 30% of eligible patients actually are being treated. Barriers include the counterintuitive nature of beta-blocker use in HF, and the complexity required of patient follow-up as well as concerns about potential adverse effects and toxicity. "The time has come to overcome these barriers and to initiate beta-blocker therapy in the large number of patients with heart failure." This should improve their quality of life and increase its length. "All patients with a left ventricular ejection fraction less than 0.40 and no contraindication to beta-blocker therapy should have beta-blockers initiated."[1]

JAMA March 8, 2000; 283: 1335-36 Editorial by Robert M Califf and Christopher M O'Connor, Duke University Medical Center, Durham, NC

Comment:

1 One indication not mentioned in previous studies concerns patients who have a low ejection fraction but are not considered to fit the definition of clinical heart failure. Early use of beta-blockers may be especially beneficial in this group. RTJ

3-4 CONSUMPTION OF NSAIDs AND THE DEVELOPMENT OF CONGESTIVE HEART FAILURE IN ELDERLY PATIENTS.

The effects of non-steroidal anti-inflammatory drugs (**NSAIDs**) are related primarily to their inhibition of prostaglandin synthesis. Prostaglandins have both vasodilator and vasoconstrictor actions. The end-result of the prostaglandin inhibition by NSAIDs is vasoconstriction, raising systemic vascular resistance, decreasing cardiac output, and lowering renal perfusion in susceptible individuals.

This study estimated the relative risk of first admission to a hospital with congestive heart failure (**CHF**) in recent users of NSAIDs compared with non-users.

Conclusion: NSAIDs raised risk.

STUDY

1. Case-control study of elderly patients (mean age 75):
   Cases — 365 patients who were admitted to a hospital with the primary diagnosis of CHF.
   Controls — 658 matched patients without CHF who were admitted to the same hospital.
2. Obtained information on use of NSAIDs.

RESULTS

1. Use of NSAIDs (other than low-dose aspirin) in the previous week was associated with a doubling of the odds of a hospital admission with CHF (odds ratio =2.1) compared with those who did not take any NSAID. Although numbers were small, the risk of CHF was also doubled in those taking regular dose aspirin.
2. Use of NSAIDs by patients with a history of heart disease increased the odds ratio for a first admission with CHF to 10.5.
3. The risk of admission with CHF was positively related to the dose of the NSAID consumed in the previous week, and was lower in those taking a short-acting NSAID (eg, ibuprofen) and increased in those taking a long-acting NSAID (eg, naproxen).

DISCUSSION

1. Assuming these relationships are causal, NSAIDs were responsible for about one of every 5 admissions for CHF.
2. "The disease burden attributable to these drugs may be large — approaching the levels of morbidity and mortality that we have previously documented for serious upper gastrointestinal complications of NSAIDs."
3. These adverse effects are likely induced by short-term hemodynamic changes through inhibition of prostaglandin synthesis.
4. "Arguably, guidelines should discourage the use of NSAIDs in individuals with a damaged but compensated left ventricle. We recommend that these drugs should be used with caution in such individuals in the lowest possible dose, and that drugs with a long plasma half-life should be avoided." (*See table 4 p 783 for a list of short- and long-acting NSAIDs.)*

CONCLUSION

The burden of illness resulting form NSAID-related CHF may exceed that resulting from GI tract damage. NSAIDs should be used with caution in patients with heart disease.

Archives Int Med March 27, 2000; 777-784 Original investigation, by John Page and David Henry, University of Newcastle, Australia.

Comment:

This is an important clinical point. The cumulative adverse effects of NSAIDs (upper gi bleeding and perforation, hypertension, renal dysfunction, and increased risk of CHF) are large nationwide,

considering the vast numbers of individuals taking them. All elderly who take them regularly should be monitored.

What about COX-2 inhibiting NSAIDs (celecoxib and rofecoxib)? The best information I have is that they also adversely affect the kidney, leading to sodium and water retention. RTJ

This is the first I remember reading about this possible adverse effect of regular-dose aspirin. Aspirin has the advantage, however of being a short-acting drug (in regard to effects on prostaglandins). I will be on the lookout for further reports. RTJ

3-5 PLANT STEROL AND STANOL MARGARINES AND HEALTH

New margarines (eg, *Benechol*) introduced recently. Others are forthcoming. They lower serum cholesterol concentrations. They are expensive.

This article considers quantitatively the health aspects of adding plant sterols and stanols to margarines and other foods.

Sterols are essential components of cell membranes of both plants and animals. The sterol ring is common to all. The differences are in the side chains. Cholesterol is exclusively an animal sterol. Over 40 plant sterols have been identified. Beta-sitosterol is one of the most abundant. It is structurally similar to cholesterol.

Stanols are saturated sterols (no double bonds in the sterol ring).

Plant sterols and stanols lower serum cholesterol by reducing absorption of cholesterol by competing for the limited space in mixed micelles (the packages in the lumen of the gut that deliver mixtures of lipids for absorption into the mucosal cells). They reduce absorption of both exogenous (dietary) cholesterol and endogenous (biliary) cholesterol by about half. This lowers serum cholesterol despite a compensatory increase in cholesterol synthesis in the liver.

An average daily consumption of butter or margarine is 25 g. The average dietary cholesterol intake is 300 mg. The average dietary intake of plant stanols is 250 mg (higher in vegetarian diets).

The new margarines contain 2 g of plant sterols or stanols (**S and S**). Very little of them are absorbed.

As long as 20 years ago, it was recognized that plant sterols and stanols could be added to foods. Because fat is needed to solubilise them, margarines are an ideal vehicle for them. Cream cheese, olive oil, salad dressings, and yogurt are also used.

The author lists a number of randomized trials that report a difference in serum LDL-cholesterol levels obtained from using polyunsaturated margarines with and without added S and S. Daily dose of the S and S varied from 0.8 g to 3.4 g. LDL was reduced by an average of 14%. (20 mg/dL;

0.54mmol/L) in subjects aged 50-59. (Less reduction in younger subjects.) The dose-response relation was continuous up to 2 g daily with no further reduction at higher doses.

There was little change in triglycerides and HDL-cholesterol.

"Data . . . indicate that in people aged 50-59, the reduction in LDL cholesterol of about 0.5 mmol/L would reduce the risk of heart disease by about 25% after about 2 years." "This is an impressive result for a dietary change that, price apart, is modest." The effect is larger than could be expected from that of a low saturated fat diet.

Despite the extensive promotion of healthy eating there has been little reduction in average serum cholesterol concentrations in many countries.

Safety: Stanol margarines have been sold in Finland for three years without evidence of hazard. The most important concern is the possible reduction in some fat soluble vitamins. Some lowering of beta-carotene and vitamin E have been reported. Blood concentrations of vitamin D were not affected.

"Plant sterols and stanols do not adversely affect the taste or consistency of margarines." **1**

Acceptance depends somewhat on personal choice after being fully informed, and considering cost, and taste, and especially risk of cardiovascular disease. Those at high risk will benefit more. S and S may appeal to persons with established ischemic heart disease, but they should not replace statins. Both, however, can be taken together. The cholesterol lowering effects of the two are additive.

No health claim can be made in the advertising of these margarines because they are a food, not a drug. "More people might buy the product if they were aware of the size of the health benefit."

"The launch of margarines containing plant sterols and stanols is a welcome first step in what may become an important innovation in the primary prevention of ischemic heart disease."

BMJ March 25, 2000; Original investigation by Malcolm Law St Bartholomew's and the Royal London School of Medicine and Dentistry, UK.

1. This would be a matter of individual preference. I found Benechol did taste differently.

It certainly did not compare with a good butter.

Dr Law states he has no competing interest. RTJ

3-6 UNDERSTANDING ECONOMIC AND OTHER BURDENS OF TERMINAL ILLNESS: The Experience of Patients and Their Caregivers.

Terminal illness imposes substantial burdens, economic and otherwise, on patients and caregivers. This study determined the mechanisms for the economic and non-economic burdens and identified potentially ameliorating interventions.

STUDY

1. Conducted in-person interviews with 1000 terminally ill patients and their caregivers in 6 randomly selected US sites.
2. Discussed needs for transportation, nursing care, homemaking, and personal care; subjective perception of economic burden; expenditure of more than 10% of household income on health care; caregiver depression and sense of interference with his or her life; and patient consideration of euthanasia and physician-assisted suicide.

RESULTS

1. Patients:
   Of all patients, 35% had substantial care needs. They were more likely to report a subjective sense of economic burden, that 10% of their household income was spent on health care, and that their families had to take out a loan or a mortgage, spend their savings, or obtain an additional job.
   They were more likely to consider euthanasia or physician-assisted suicide.
2. Caregivers:
   Were more likely to have depressive symptoms, and report that their caring interfered with their lives.
   Those who reported that the physicians they dealt with listened to the needs and opinions [of the caregiver] about the patient's illness or medical treatment were significantly less likely to be depressed than caregivers who dealt with physicians who did not listen.

DISCUSSION

1. Poor physical function, incontinence, older age, and low income were associated with greater care needs. But these factors are not readily modifiable or amenable to medical interventions.
2. "It seems that physicians can reduce caregivers' depression simply by listening well."
3. Previous surveys have reported that patients' fear of being a burden is a primary motivation for inquiries about euthanasia and physician-assisted suicide.

CONCLUSION

Substantial care needs are an important cause of the economic and other burdens imposed by terminal illness. Through empathy, physicians may be able to ameliorate some of these burdens.

Annals Int Med. March 21; 2000; 132: 451-59 Original investigation, first author Ezekiel J Emanuel, National Institutes of Health, Bethesda MD.

Comment:

This emphasizes the oft-repeated message about stress experienced by care-givers. As the article points out, listening compassionately to their concerns may relieve some of the distress. But, attending physicians can do more to alleviate patient and family burdens than by listening. (Admittedly, listening and expressing empathy are helpful in their own right.) Primary care physicians can help gain assistance from Hospice. We should be familiar with all community services available to aid families and patients, how to access them. We can encourage families to spread the burden among all family members (rather than placing it all on the resident daughter). We can encourage regular vacations be taken by chief caregivers. And can help by hospitalizing patients when reasonable and acceptable or by suggesting placement in a long-term care facility. RTJ

RECOMMENDED READING

3-7 DEATH AND THE RESEARCH IMPERATIVE

We are aware of the often harmful effect in caring for dying patients caused by the "technological imperative"— that is, the compulsive use of technology to maintain life when palliative care would be more appropriate. 'There is another imperative that now deserves attention in assessing the care of the dying — the "research imperative". This stems from the view that medicine has an almost sacred duty to combat all the known causes of death — that death is the principal evil of human life.

"At the heart of modern medicine is a conflict about the place and meaning of death in human life." The conflict pits the underlying logic of the research imperative, which is to overcome death itself, against the newly emergent (although ancient) clinical imperative to accept death as part of life and to make dying as tolerable as possible. Death was not considered the enemy by ancient medicine. The cultural and religious focus was on finding a meaning for death, on giving it a comprehensible place in human experience, and on making the passage from life to death as comfortable as possible.

Now, ". . .death is still denied, evaded, and, in the case of many clinicians, fought to the end, regardless of the patient's wishes."

The tacit message of the research agenda is that, if death itself cannot be eliminated, then at least all the diseases that cause death can be done away with. (Ie, to eliminate death, disease by disease.) The research imperative to fight death stands foursquare against fatalism, against giving up hope, and against thinking that nature cannot be brought to heel.

The ethicist-essayist presents several strategies to ameliorate the conflict:

1) Promote the idea that research should focus on *premature* death.

2) Give the "compression of morbidity" (a shortening the period of poor health before death) a research status equivalent to that now given to the prolongation of life. "It is not death that is the enemy, but a painful, impaired, and unhealthy life before death."

3) Persuade clinicians that helping a patient have a peaceful death is as important an ideal as averting death. The two ideals should be given equal value: physicians ought to be as anxious to avoid a poor death and to extend life. Since we all die, the preservation of life should not be understood as necessarily a higher ideal than a peaceful death. Palliative care should be aimed at all of us, not just the patients whom medicine cannot save.

4) Redefine medical progress. Medical progress is now commonly understood to be the conquest of lethal disease and an increase in life expectancy. In the case of premature death it should. But with advances in medicine and public health increasing the likelihood of long lives, progress should be redefined as the prevention of illness and disability, the successful management of disability, a reduction in conditions that do not cause death but do ruin lives (eg, serious mental disorders), and successful efforts to help people understand how to remain healthy.

"We can change the way people are cared for at the end of life, and we can substantially reduce the burden of illness. It is not, after all, death that people seem to fear the most, and certainly not old age, but a life poorly lived. Something can be done about that."

NEJM March 2, 2000; 654-56 "Sounding Board", commentary by Daniel Callahan, Hastings Center Garrison, NY.

REFERENCE ARTICLE

3-8 MEDICAL TERMINATION OF PREGNANCY

"Termination of pregnancy has been practiced since antiquity." An estimated 26 million pregnancies are terminated legally each year throughout the world; and 20 million illegally, with more than 78 000 deaths. "A safe medical method would save many lives."

The US has one of the highest abortion rates among developed countries, yet approximately 86% of US counties had no abortion providers or facilities. "Indeed, access to abortion is becoming increasingly difficult in the United States because of the harassment of both patients and health care personnel outside abortion facilities.. The number of physicians who perform abortions has decreased.

"The availability of safe drugs for the termination of pregnancy would be of immeasurable value for women and the medical profession."

Implantation of a fertilized ovum (embryo) involves complex interactions with the endometrium. The embryo becomes attached to the endometrium on day 6 to 10 days after ovulation. This depends on

progesterone. Drugs used to terminate pregnancy act by antagonizing the action of progesterone (mifepristone; RU 486), inducing myometrial contractions (prostaglandins; eg, misoprostol), or inhibiting the development of the trophoblast (methotrexate).

The article comments on mode of action, efficacy, and adverse effects of each.

Medical termination can be performed as soon as the pregnancy has been confirmed. It is not recommended after 9 weeks of gestation because of the high incidence of failure and uterine bleeding. Success depends on the duration of pregnancy.

Medical abortion requires more clinic visits than surgical abortion. Methotrexate or mifepristone can be given in the clinic and the patient sent home. She usually returns to the clinic to take the prostaglandin. Then the patient may wait under observation for 3 to 6 hours to determine outcome. Some women find this burdensome. If abortion fails or results in incomplete abortion or excessive bleeding, surgical termination is performed.

Medical termination is acceptable to the majority of women. Most say they would choose it over surgical abortion if facing the choice again. However, for pregnancies over 50 days, medical abortion is more painful and less effective than surgery, so the latter may be more acceptable.

Mifepristone (RU 486) has been approved by many countries worldwide for termination of pregnancy. The U.S. FDA has granted mifepristone approvable status. **1**

The combination of methotrexate and misoprostol has *not* been approved by the US FDA for medical abortion, but is widely available and inexpensive.

Early in pregnancy medical abortion has a high rate of success. It is safe and acceptable to women. It does not require anesthesia. It should be offered only by well trained clinicians who can provide surgical treatment if the medical abortion fails or excessive bleeding occurs. Surgical abortion has the advantages of less prolonged bleeding, less nausea and vomiting, and less pain. It also has a higher success rate than medical abortion.

"Contrary to expectations, the legalization of abortion has not been associated with an increase in the demand for abortion."

NEJM March 30, 2000; 342: 946-56 "Drug Therapy" review article, first author Sophie Christin-Maitere, Universite Pierre et Marie Curie, Paris, France.

Comment:

Mifepristone? Misoprostol?

The terms are confused with each other. I rely on a mnemonic — mi**F**epristone (the progesterone inhibitor; F denotes female). Mi**S**oprostol (the prostaglandin use to protect the stomach against NSAIDs; S denotes stomach.)

1 My PDR does not list mifepristone.

One small study reported successful termination by use of tamoxifen (a selective estrogen receptor modulator).

REFERENCE ARTICLE

3-9 DECISION ANALYSIS AND GUIDELINE FOR ANTICOAGULANT THERAPY TO PREVENT STROKE IN PATIENTS WITH ATRIAL FIBRILLATION

Anticoagulant therapy decreases risk of embolic stroke in patients with non-valvular atrial fibrillation (**AF**). The therapy is underused in clinical practice. However, not all patients with AF will benefit from anticoagulation. Not all patients who might benefit will decide on a basis of personal preference not to accept or sustain anticoagulation.

Decision analyses can lead to development of clinical guidelines.

Clinical guidelines are needed on whether or not to use anticoagulant therapy.

This study presents a decision analysis regarding warfarin therapy in patients with AF, and develops guidelines for use based on benefit or no-benefit. Decision analysis permits explicit *quantitative* comparisons of benefits and risks of different therapies.

Conclusion: Depending on risk factors other than AF itself, the analysis presents explicit advice about benefits (or no benefits) of anticoagulation to prevent ischemic stroke.

STUDY

1. Based on a systematic literature review of patients with non-valvular AF, the authors developed a decision model about benefits of anticoagulation in prevention of stroke. The analysis included patients' estimates of the quality of life associated with different states of health and estimation of costs.
2. Risk factors included age, systolic BP, diabetes, hypertension or history of treatment for hypertension, smoking, presence of cardiovascular disease, and left ventricular hypertrophy — all in various combinations.
3. Constructed 12 decision tables (clear benefit, no benefit, or borderline benefit) incorporating the risk factors.
4. If the patient had 3 or more risk factors, or was male with left ventricular hypertrophy and one other risk factor, or had a history of minor stroke or TIA, warfarin was prescribed. Otherwise, the tables were used to determine if warfarin would benefit, was of borderline benefit, or would not benefit.

RESULTS

1. At any age, and for any systolic BP up to 170 in men and 160 in women, the tables indicate no benefit if *no* other risk factors are present.
2. Ninety seven percent of women with AF older than 75 years, and 69% of those age 65-74 would have been recommended for treatment. For men the corresponding figures were 75% and 53%.

(*For illustration of categories of clear benefit, borderline benefit, and no benefit see pp 959 and 960.)*

3. When benefit was indicated, warfarin treatment would decrease health care costs and increase quality adjusted life-years. .

DISCUSSION

1. The analysis clarified the factors affecting clinical decisions on anticoagulation in patients with non-valvular AF. (Decision-analysis explicitly quantifies uncertainty.)
2. The decision analysis allowed incorporation of a wide range of available "evidence" including patients' utilities [preferences] and the risk factors for stroke into development of a guideline . "We cannot assess individual risk or likely response to treatment other than by applying such probabilistic population-based measures. However, patient's preferences are quintessentially an individual rather than a population attribute."
3. Evidence for effectiveness of aspirin in prevention of stroke in patients with non-valvular AF is much less robust than for warfarin. The investigators used aspirin as the alternative treatment when warfarin was contraindicated, not accepted by the patient, or considered of no benefit.
4. "Our work has further emphasised the importance of incorporating patients' values into decisions. We believe that our summary guidelines, along with guidance on taking account of patients' preferences, offer a valuable tool for clinical practice."

CONCLUSION

Decision analysis was useful in the incorporation of complex probabilistic data into informed decision-making, the identification of factors influencing such decisions, and the subsequent development of evaluative guidelines for treatment of non-valvular atrial fibrillation.

See tables pp 959-960 for explicit recommendations for or against warfarin anticoagulation.

Lancet March 18, 2000; 355: 956-62 Original investigation, first author Richard Thompson, Newcastle Medical School, Newcastle Upon Tyne, UK

Comment:

Why did I spend so much time on this abstract? I believe models such as this are further removed from an individual patient than are the quantitative estimates of systematic reviews of evidence-based medicine. Nevertheless, models can give some guidance and help patients arrive at a preference for or against treatment.

The tables on pp 959 and 960 are explicit and easy to understand. Note that the decision model will lead to use of warfarin in the great majority of patients. But *not* in any patients at any age with no risk factors.

Aspirin should be advised when warfarin is not acceptable. RTJ

3-10 LIKELIHOOD RATIOS

Last month I reviewed the concepts of sensitivity, specificity, and predictive values. This is a continuation — the second step in determining the reliability of diagnostic tests. The third step, application of Bayesian statistics follows next month. RTJ

There are 2 likelihood ratios of diagnostic tests for a disease or target disorder:

1. *THE LIKELIHOOD RATIO OF POSITIVE TESTS:*

1) Is simply the ratio between

A. True positive tests (expressed as a percentage), and

B. False positive tests (expressed as a percentage).

a. If the ratio of true positive tests to false positive tests is higher than 1:1, (more true positives than false positives) a positive test indicates a higher probability that the disease in question is present.

b. If the ratio of true positive tests to false positive tests is lower than 1:1 (more false positives than true positives) a positive test indicates a lower probability that the disease in question is present.

c. If the ratio is 1:1 a positive test is not helpful because it is just as likely to be positive when the disease is not present as it is to be positive when the disease is present.

2) Three easy steps to determine the likelihood ratio of positive tests:

A. Determine the *percentage* of patients *with the disease* who have a positive test — the true positive percentage. (Note: this is the sensitivity of the test.)

B. Determine the *percentage* of patients *without the disease* who have a positive test — the false positive percentage. (Note: this is 100% minus the specificity of the test.)

C. Divide A by B to obtain the ratio.

Example:

In the 2 X 2 table in abstract "The Role of Clinical Suspicion in Evaluating a New Diagnostic Test for Active Tuberculosis" in the February 2000 issue of *Practical Pointers:*

	Low clinical suspicion (n=224)	
	TB present (n=12)	TB absent (n=212)
E-MTD positive	10 (True positive = 84%)	7 (False positive = 3%)

E-MTD negative	2	205

(Note that likelihood ratio of positive tests is determined by numbers on the top row. In this study, the E-MDT positive row)

A. The percentage of patients who have TB who have a positive test is 10/12 = 84% (true +)

B. The percentage of patients who do not have TB who have a positive test is 7/212 = 3% (false +)

C. Divide A by B — 84%/3% = 28. This is the likelihood ratio of positive tests *for this test run in this cohort* of patients. Ie, if the test is positive, it is 28 times more likely that the patient does indeed have TB as it is that he does not have TB.

2. *THE LIKELIHOOD RATIO OF NEGATIVE TESTS:*

1) Is simply the ratio between

A. False negative tests (expressed as a percentage), and

B. True negative tests (expressed as a percentage).

a. If the ratio of false negative tests to true negative tests is higher than 1:1 (more false negative tests than true negative tests), a negative test indicates a higher probability that the disease in question is present.

b. If the ratio of false negative tests to true negative tests is lower than 1:1 (more true negatives than false negatives) a negative test indicates a higher probability that the disease in question is *not* present.

c. If the ratio is 1:1 a negative test is not helpful because it is just as likely to be negative when the disease is present as it is when the disease is not present.

2) Three easy steps to determine the likelihood ratio of negative tests:

A. Determine the *percentage* of patients *with the disease* who have a negative test—the false negative percent. (Note: this is 100% minus sensitivity of the test.)

B. Determine the *percentage* of patients *without the disease* who have a negative test — the true negative percent. (Note: this is the specificity of the test.)

C. Divide A by B to obtain the ratio.

Example:

In the 2 X 2 table in abstract "The Role of Clinical Suspicion in Evaluating a New Diagnostic Test for Active Tuberculosis" in the February 2000 issue of *Practical Pointers:*

	Low clinical suspicion (n=224)	
	TB present (n=12)	TB absent (n=212)
E-MTD positive	10	7

E-MTD negative 2 (false negative = 16%) 205 (true negative = 96%)

(Note that likelihood ratio of negative tests is determined by numbers on the bottom row, the E-MDT negative row)

A. The *percentage* of patients who have TB who have a negative test is 2/12 = 16% (False negative tests)

B. The *percentage* of patients who do not have TB who have a negative test is 205/212 = 96% (True negative tests)

C. Divide A by B — 16%/96% = 0.16. This is the likelihood ratio of negative tests for *this test in this cohort* of patients. Ie, if the test is negative, it is only 0.16 times as likely that the patient does have TB as it is that he does not have TB. (Six times more likely that he does not have TB as it is that he has TB.)

I was guided in preparing this article by a small volume "Evidence-based Medicine; How to Practice and Teach EBM", Churchill Livingston, first author David L Sackett. RTJ

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3-11 CIGARETTE SMOKING AND INVASIVE PNEUMOCOCCAL DISEASE

The incidence of invasive pneumococcal disease (**IPD**) is highest among young children and the elderly. Although the relative rates are lower among younger adults, the absolute numbers of IPD is highest in this group. Up to 1/3 of adults with IPD have no recognized risk factors.

This study investigated the importance of smoking as a risk factor for IPD.

Conclusion: Smoking was the strongest independent risk factor for IPD.

STUDY

1. Population-based study identified 228 patients between ages 18 and 64. who had a history of IPD. Fifteen percent were age 18-29; 54% age 30-49; 31% age 50-64. All were immunocompetent.
2. Defined IPD as the isolation of *Streptococcus pneumoniae* from a normally sterile site (blood, meninges).
3. Matched these patients (cases) with 301 controls selected randomly.
4. Compared rates of smoking between the 2 groups.

RESULTS

1. Fifty eight percent of the case patients were current smokers vs 24% of controls.
   Odds ratio = 4 (smokers vs non-smokers).
2. Non-smokers who were passively exposed to cigarette smoke were also at higher risk.
   Odds ratio = 2.5. Risk increased as the duration of exposure increased.

3. Risk increased with the number of cigarettes smoked daily and the number of pack-years smoked.
4. Risk decreased as the time since cessation of smoking increased.
5. The adjusted population attributable risk of IPD was 51% for smoking, 17% for passive smoking, and 14% for chronic illness.

DISCUSSION

1. Cigarette smoking was the strongest independent risk factor for IPD —statistically, about half of the disease burden in this group of otherwise healthy immunocompetent persons age 18-65.
2. Risk was dose-dependent.
3. Increased risk was also independently associated with exposure to environmental smoke.
4. Cigarette smoke impairs mucociliary clearance, enhances bacterial adherence, and disrupts the respiratory epithelium.
5. Higher rates of nasopharyngeal colonization with meningococcus, as well as the pneumococcus, have been observed among active and passive smokers. Smokers are also more susceptible to viral infections, such as influenza. A recent upper respiratory infection can increase the risk of IPD. In addition, pneumococcal disease is more common in patients with COPD, probably because of defective clearance mechanisms. However, COPD was not common in this cohort.
6. Fewer than 1/3 of persons in the cohort had a condition for which pneumococcal vaccine is recommended.
7. Immunocompetent patients benefit from pneumococcal vaccine. “It may be reasonable to incorporate the pneumococcal vaccine into smoking cessation programs as well as to consider vaccinating those who continue to smoke.”

NEJM March 9, 2000; 342: 681-89 Original investigation, first author J Pekka Nuorti, Centers for Disease Control and Prevention, Atlanta, GA

Comment:

This was a study of healthy immunocompetent adults. Children and the elderly were excluded. They present a different problem.

The comment about meningococcal disease intrigued me. Students returning to school in the fall are more frequently colonized by the meningococcus at this time. I would advise my child to avoid a room-mate who smokes. RTJ

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3-12 SMOKING AND PNEUMOCOCCAL DISEASE

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

Smoking kills. Tobacco use was responsible for approximately 1/5 of all deaths in the United States in 1990. Deaths due to cardiovascular disease, cancer (especially the lung) and chronic obstructive pulmonary disease were among those attributable in part to smoking.

The study adds invasive pneumococcal disease to the grim list of diseases associated with smoking.

Smoking enhances the binding of *S pneumoniae* to pharyngeal cells, damages local defenses by impairing mucociliary flow, increases permeability of the respiratory epithelium, reduces humoral responses to inhaled antigens, and increases susceptibility of the host to respiratory viruses.

The study provides the best evidence to date that smoking promotes pneumococcal disease and establishes smoking as the most important risk factor for invasive disease among immunocompetent, non-elderly patients.

Only 10% of the patients had been vaccinated against the pneumococcus. Unfortunately, in the patients for whom it is currently indicated, the efficacy of the pneumococcal vaccine in suspect, and doubts about its efficacy have contributed to the low rates of vaccination. In the successful prelicensure vaccine trials, the subjects were young and generally healthy, but in more recent randomized trials, vaccination has failed to prevent pneumonia and invasive disease in high-risk older patients. (*Likely due to blunted immune response. RTJ*)

Vaccinating immunocompetent, non-elderly smokers may be reasonable. Such persons are healthier and may respond better to vaccination than the high-risk patients for whom the vaccine is currently considered to be indicated.

Physicians should double their efforts to promote smoking cessation. A physician's advice to stop is powerful and should be offered to every patient. Physicians should help smokers set a quitting date and should arrange for follow-up shortly thereafter. Counseling programs, nicotine replacement, and bupropion (*Zyban*) alone or in combination can improve long-term success rates.

"Patients looking for additional motivation now have another reason to stop smoking."

NEJM March 9, 2000; 342: 732-34 Editorial by John V L Sheffield and Richard K Root, Harborview Medical Center, Seattle, WA

Comment:

Patients at risk should be immunized when they are immunocompetent. This includes smokers, whether they stop or not. I believe the elderly should receive vaccine before they get too old and unresponsive. And many should be revaccinated. RTJ

3-13 CHANGING CARRIAGE RATE of *NEISSERIA MENINGITIDIS* AMONG UNIVERSITY STUDENTS DURING THE FIRST WEEK OF TERM

In the past decade, there have been increases in the incidence of invasive meningococcal disease in many developed countries, especially among teenagers and young adults. Serogroup C is the most common pathogen. University undergraduates have higher rates of invasive meningococcal disease than young adults of the same age not attending.

This study determined the rates of, and risk factors for, meningococcal carriage among university students.

Conclusion: Carriage rates increased rapidly during the first week of attendance.

STUDY

1. Cross sectional study followed over 2500 students during their first year at university.
2. Cultured multiple pharyngeal swabs for *N meningitidis.*

RESULTS

1. Carriage rates: Day 1 of term = 7%; day 2 = 11%; day 3 = 19%^; day 4 = 23%.
2. Carriage rates were higher among students attending dining halls, reaching 34% by December.
3. Independent associations for acquisition of the meningococcus: frequency of visits to a bar; active and passive smoking; being male; intimate kissing.
4. Lower rates occurred in female-only halls. Students living off campus were less likely to be carriers.

DISCUSSION

1. During the first month of university term, carriage rates increased rapidly — most of this during the first week. (From about 8% to 23%)
2. Rapid acquisition rates have also been reported in military recruits.
3. Social mixing (congregating in bars and halls) was a risk factor
4. Non-grouped strains and serogroup B were common. Serogroup C was also common, and some of the strains were known to be virulent. (Highly virulent clones transmit readily person to person.)
5. Vaccine is effective in preventing group C invasive disease.
6. The high rates of carriage explains the higher rates of invasive disease reported among students each autumn during the first term of university .
7. "Our findings support the introduction of meningococcal vaccine for university students."

CONCLUSION

Carriage rates of meningococci among university students increases rapidly during the first week of term, with further increases during the term. This increases risk of invasive disease.

BMJ March 25, 2000; 846-49 Original investigation, first author Keith R Neal, University of Nottingham, UK

Comment:

This is an important clinical point which at times may be life-saving. I would advise my student-child to avoid smoking and choose a non-smoking room-mate. Also to avoid crowding and intimacy as much as possible.

Parents, faculty, and student health workers should be attuned to the possibility that their students and children will likely be exposed to the meningococcus early in the term, and should be willing to advise immediate intramuscular penicillin in case of a serious febrile illness. RTJ

3-14 A PROSPECTIVE STUDY OF HOLIDAY WEIGHT GAIN

Overweight and obesity are national problems, affecting approximately half of the US adult population. The proportion of people with a body mass index over 30 has increased by 50% in the past decade.

Once established, obesity is difficult to reverse.

Understanding times when people are more likely to gain weight throughout life is important for the development of preventive strategies. Adolescence, pregnancy, midlife in women, and the period after marriage in men appear to be times of susceptibility to weight gain. Cessation of smoking and emigration to a more highly urbanized culture are also risk factors.

For most adults, there is a slight increase in weight over time, ranging from 1/2 to 2 pounds per year. A national survey reported body weight in young adults increased an average of 3.4% in men and 5.2% in women over a 10 year period.

Is this gain due to small steady increases in weight throughout the year, or to small increases during discrete periods (such as holiday seasons) when energy intake may increase or energy expenditure may decrease?

In the US, the winter holiday season is generally considered to begin with Thanksgiving and end on New Year's Day. Weight gain has been associated with this period, variously reported by the lay press as an average of 5 to 10 pounds. None of the reports cited a credible source for that suggestion. Indeed, a literature search failed to identify any clinical research findings supporting the claim.

This study determined the effect of both the season and holiday period on changes in body weight in US adults.

Conclusion: On average, there is weight gain during the holiday season and in the winter, but the amount gained is less than commonly asserted. The gain is not reversed later in the year.

STUDY

1. Measured the actual holiday-related weight variation in 195 healthy adults. All subjects were weighed at intervals over 6 to 8 weeks during 3 periods: preholiday (September, October, early November); holiday (mid November to mid January); and postholiday (mid January to early March).

2. Made a final weight measurement the following September or October.

RESULTS

1. Mean weight increased significantly during the holiday period but not during the pre-holiday season or the post-holiday period:

	Kg	Pounds
Holiday	+ 0.37	+0.8
Pre holiday	+ 0.18	+0.4
Postholiday	- 0.07	- 0.15 (loss)
Fall to spring	+0.48	+1.0
Spring to fall	+0.21	+0.5

(*The standard deviations were wide — + or – 1.5 to 2 kg. Ie, some gained much more; some actually lost weight. See figure 1 p 863 for an illustration of mean weight changes*.)

2. Subjects who were overweight or obese at baseline were much more likely to have a major weight gain during the holidays. (*See figure 23 p 864.)*
3. Many subjects reported they were less active and more hungry during the holidays.

DISCUSSION

1. The weight change during the holiday season was much less than usually reported. Indeed, less than most subjects estimated they had gained. Fewer than 10% gained over 5 pounds. This despite the fact that the great majority of subjects made no attempt to control their weight.
2. However, the weight that was gained was largely maintained during the rest of the year.
3. The period contributing most to yearly weight gain was the six-week holiday.
4. Those subjects who gained the most were overweight or obese at baseline. Weight reduction and weight maintenance programs are less effective during the holidays.
5. "These results suggest that the winter holiday season may present special risks for those who are already overweight or obese and that such persons may benefit from seasonal efforts to prevent weight gain."
6. The data suggest that the holiday weight gain is not reversed during the spring and summer. Therefore, the cumulative effects of a yearly weight gain during the holidays are likely to contribute to the substantial increase in weight that frequently occurs over the years in adulthood.

CONCLUSION

The average weight gain during the winter holiday season is less than commonly asserted. But, the gain is not reversed during the following spring and summer. Thus the average gain of about 1 pound in the fall and winter contributes to the cumulative increase in weight during adulthood.

NEJM March 23, 2000; 861-6y "Special Article" original investigation, first author Jack A Yanovski, National Institute of Child Health and Human Development, Bethesda MD.

Comment

Many outliers gained much more weight than average. They require special attention.

Is this article worth abstracting? After all, we intuitively would arrive at much the same conclusions. I believe it does present an important clinical point which can be helpful for those of us who are health conscious. I doubt if many individuals would or should deny themselves the pleasure of family feasts and cheer during the holidays. This is one of our greatest pleasures. We can. however, attempt to be prudent and make a conscious effort to increase physical activity during these seasons. By increasing exercise and modestly decreasing energy intake during the holidays, one may more likely maintain a constant weight during the year. RTJ

3-15 TUMOR NECROSIS FACTOR BLOCKERS IN RHEUMATOID ARTHRITIS

"For patients with rheumatoid arthritis, a new era of treatment has begun." This optimistic view reflects the introduction of tumor necrosis factor (**TNF**) blockers.

TNF is a cytokine, a product of macrophages. It exerts powerful effects on the immune system, including induction of pro-inflammatory mediators (eg, interlukin-1, nitric oxide, and prostaglandins), metalloproteinases, and adhesion molecules. It has physiological functions in host defense.

TNF has a pivotal role in the pathogenesis of rheumatoid arthritis (**RA**).

Now 2 man-made TNF inhibitors are available:

1) Infliximab (*Remicade*), a chimeric monoclonal antibody to TNF, has the variable region of a murine antibody grafted into the constant region of a human antibody. (25% mouse; 75% human).
2) Etanercept, a soluble receptor for TF, is a designer molecule – a dimer consisting of a TNF receptor joined to the Fc domain of a human IgG molecule. (5% mouse; 95% human). It also binds another cytokine, lymphotoxin-alpha, as well as TNF.

Both bind TNF and inhibit its downstream effects.

In treatment of adult RA the blockers have rapid, substantial, sustained benefits even in patients who have not responded to other anti-rheumatic drugs including methotrexate.

The variety of effects of TNF raises the specter of side effects when its physiological effects are blocked. TNF is a key player in host defense. Blockers should be used with caution in patients with infection. They should be discontinued when serious viral or bacterial illness occurs. Thus far, however, TNF blockers have been reported as safe.

Although juvenile RA differs from adult RA, and presents in several different ways, study of etanercept in this issue of NEJM[1] reports significant benefit.

The blockers are expensive. The sequence of their use, or safety and benefits of use combined with other anti-inflammatory agents remains to be determined.

NEJM March 16, 2000; 342: 810-11 Editorial by David S Pisetsky, Duke University Medical Center, Durham NC

1 "Etanercept in Children with Polyarticular Juvenile Rheumatoid Arthritis" NEJM March 11, 2000; 342: 783-89

See also: "Antibodies to Tumor Necrosis Factor alpha as Treatment for Crohn's Disease." Lancet March 11, 2000; 355: 858-60

REFERENCE ARTICLE

3-16 THERAPEUTIC MONOCLONAL ANTIBODIES

Monoclonal antibodies (mAb) are antibodies produced by a single clone of B cells. They are monospecific and homogenous. Originally they were produced by immunizing mice against a specific antigen, then fusing the mice B cells to human myeloma cells. This produces a hybridoma which is immortalized and can be produced in unlimited quantities. The mAb (an immunoglobulin) produced is chimeric (human Fc domain fused to a mouse Fab domain). Now completely humanized mAb can be produced. (*See figure p 735*)

At present, a number of mAbs are registered for therapeutic use: renal graft rejection, rheumatoid arthritis, Crohn's disease, antiplatelet activity, and antiviral activity. Application of mAbs may be widespread, including treatment of cancers.

Lancet February 26, 2000; 355: 735-40 Review article, "New Drug Classes" by F C Breedveld, Leiden University Medical Center, Leiden, Netherlands.

Comment:

Not a valid practical point for primary care at this time, but provocative enough to call to our attention. RTJ

REFERENCE ARTICLE

3-17 GUIDELINES ON PREVENTING CARDIOVASCULAR DISEASE IN CLINICAL PRACTICE.

(*This theme issue of BMJ presents articles concerning risk of cardiovascular disease. The data presented are*

too exhaustive to abstract concisely. It includes three different tables which give detailed absolute risks depending on age, sex, diabetes, blood pressure, smoking, and HDL/total cholesterol ratios. The predictions are derived from the Framingham Heart Study.

All three can be easily retrieved from www.bmj.com by citing the volume and first page. (See citations below.) Primary care clinicians and their patients now have valid means of assessing risk of cardiovascular disease and taking preventive measures. RTJ)

Ten years ago, clinical recommendations on preventing cardiovascular disease focused primarily on managing individual risk factors, particularly raised blood pressure and cholesterol concentrations. Typically, separate guidelines were developed for each risk factor, and treatment was recommended when that factor was above a specified level. These recommendations were based mainly on evidence from cohort studies showing increased relative risk of cardiovascular disease in people with raised levels of the risk factor and by evidence of trials showing relative benefits from lowering the factor.

"Over the past decade, we have witnessed a remarkable change from these recommendations based on relative risk to ones based on absolute risk."

"All policy decisions should be based on absolute measures of risk; relative risk is strictly for researchers only" Geoffrey Rose

Priority for treatment should be given to patients at high absolute risk of coronary heart disease (**CHD**), defined as the probability of developing CHD over a specified period (5, 10, 15. 30 years) rather than undue emphasis being placed on an individual risk factor. (Patients with established CHD are not included in the tables. They require cardioprotective drug treatment in addition to lowering risk factors.)

The absolute benefits of treatment are directly proportional to the pretreatment risk over a wide range of age and risk factors. The absolute risk of cardiovascular disease is strongly influenced by the *combination* of risk factors present, particularly age, gender, diabetes, smoking, blood pressure, and lipid concentrations.

It would seem preferable to target cardiovascular disease rather than CHD risk. As the 2 measures of risk are strongly correlated, multiplying coronary risk by 4/3 will give a reasonable estimate of overall cardiovascular risk.

BMJ March 11, 2000; 320: 659-61 Editorial by Rodney Jackson, University of Auckland, New Zealand.

1. "Coronary and Cardiovascular Risk Estimation for Primary Prevention: Validation of a New Sheffield Table" BMJ March 11, 2000; 320: 671-76
2. "Joint British Recommendations of Prevention of Coronary Heart Disease in Clinical Practice" BMJ March 11, 2000: 320: 705-08 In addition to the coronary risk reduction chart, this comments on lifestyle targets for all patients, and targets for blood pressure, lipids, and diabetes. Also cardioprotective drug treatment and screening of first degree relatives.

3. “Updated New Zealand Cardiovascular Disease Risk-benefit Prediction Guide’ BMJ March 11, 2000; 320: 709-10

3-18 ESTIMATING CARDIOVASCULAR RISK FOR PRIMARY PREVENTION: Outstanding Questions For Primary Care

(*This article comments on some of the aspects of the preceding* article.)

Individuals with established cardiovascular disease are excluded from these risk calculations. They are already at high risk and should receive measures to reduce all risk factors possible.

Prediction of coronary risk on the basis of multiple risk factors is more accurate than with any single factor alone.

It is important to be clear which outcome is being predicted and over what period. Expressed as risks at one, five, or ten years, the predicted outcomes include fatal and non-fatal coronary heart disease, stroke, and total cardiovascular disease (including cardiac failure and peripheral vascular disease). The risk of a coronary heart disease event over 10 years (myocardial infarction deaths, non-fatal myocardial infarction, and angina) has been adopted as the standard in both Britain and the US.

The prediction rules are more accurate at older than at younger ages. And most accurate when the ratio of total cholesterol to high-density cholesterol is used. They then correctly identify 85% of the people who develop coronary heart disease.

For any given individual with diabetes (diabetes not defined) the multifactorial equations are better predictors of risk than is diabetes alone.

Risk assessment aids, rather than replaces, clinical judgement. Individual factors should be considered alongside risk predictions. Relative risk rather than absolute risk remains a key factor in determining lifestyle advice, particularly in young people

A 30% risk of a coronary event over 10 years would identify 3.4% of the population aged 35-69 years who would benefit from preventive drug therapy — to which a further 4.8% of the population with pre-existing coronary heart disease should be added to make a total of 8.2%. If these criteria were adopted nationally, costs would be substantial. Lowering the threshold to 15% over 10 years would involve 25% of the population in treatment decisions for aspirin and statins — to which should be added people with blood pressures of 140-149/90-99 requiring antihypertensives. At the 15% -5 year coronary event threshold, 60 people would be exposed risks of drug treatment for 5 years to avert one coronary or stroke event.

The evidence of reduced mortality with thiazides and reduced cardiovascular events with beta-blockers in people with raised blood pressure is substantial. For mild hypertension, at a 15%- 5 year risk of a coronary event, 40 people would need to be treated with thiazides or beta-blockers for 5 years to

avert one coronary or stroke event. Several major double-blind trials found that thiazides and beta-blockers are not associated with more adverse effects than placebo. And quality of life was *enhanced* in the treatment groups.

BMJ March 11, 2000; 320: 702-04 "Education and Debate", Commentary, first author John Robson, St Bartholomew's and the Royal London School of Medicine and Dentistry, London, UK

Comment:

Much of commentary in these risk-assessment studies was slanted toward national policy—at what level of risk should national guidelines recommend drug therapy. (Lifestyle therapy is recommended for all.) This involves calculations of costs both for the drugs themselves as well as care of any adverse effects they cause.

Recommendations for individuals are entirely different. They depend on the individual receiving full information on the benefit/harm-cost of drug interventions, then making a personal choice. RTJ

3-19 GLUCOSAMINE AND CHONDROITIN FOR TREATING SYMPTOMS OF OSTEOARTHRITIS

Glucosamine is a hexosamine sugar (NH2 replacing OH in the hexose)— a basic building block of glycans (polysaccharides) that are important constituents of articular cartilage. Chondroitin is a glycosaminoglycan (a muco[protein]polysaccharide) found in cartilage. Both can be derived from animal products and can be used therapeutically. Both are termed "*nutraceuticals*" (ie, foods having pharmacological effects).

Their mechanism of action in the treatment of osteoarthritis (OA) is not known.

This issue of JAMA reports a systematic review[1] of randomized, controlled trials (**RCTs**) of glucosamine and chondroitin (used separately, not together). The main finding was that both are likely to be effective therapies for the symptomatic management of OA. However, the degree of clinical benefit may be less than that predicted by the RCTs because of methodological flaws (inadequate allocation concealment; absence of intention-to-treat analyses) and probable publication bias. There was an inverse relationship between trial size and quality of the study, which indicate a likely exaggeration of treatment benefits.

Publication bias (the greater likelihood that research with statistically significant results will be published compared with research with non-significant results) tends to produce exaggerated treatment benefits. The systematic review found that only 1 of 15 RCTs was deemed completely independent in terms of manufacturer. This raises suspicion of publication bias. (RCTs supported by the pharmaceutical industry may be associated with publication bias, a biased interpretation of results, or both.)

Funnel plots display effect size vs the number of patients enrolled in the study (*see figure 2 p 1473*). If a greater effect size is found in studies with fewer patients enrolled, this creates an asymmetrical funnel plot and suggests that smaller trials with negative results are not published.

The toxic effects of the nutraceuticals were not summarized. Long-term efficacy and safety have not been established.

The relative purity and content of the substances in different preparations made by different manufacturers may vary. Thus, the relative efficacy and toxicity may vary.

"As with many nutraceuticals that currently are widely touted as beneficial for common but difficult-to-treat disorders, the promotional enthusiasm often surpasses the scientific evidence supporting clinical use."

JAMA March 15, 2000; 1483-84: Editorial by Tanveer E Towheed, and Tassos P Anastassides, Queen's University, Kingston, Ontario, Canada.

Comment:

1 "Glucosamine and Chondroitin for Treatment of Osteoarthritis: A Systematic Quality Assessment and Meta-analysis" JAMA March 15, 2000; 1460-75 Six glucosamine and 9 chondroitin trials are cited. Only one was independent of the manufacturer. The article also comments on the difference between allocation concealment and blinding. *Allocation concealment* is separately assessed from blinding. The primary investigators take adequate measures to conceal allocation to study groups from those who assess patients for entry into a trial. This includes central randomization, sealed envelopes, coded bottles, drugs prepared by the pharmacy. It relates to preventing selection bias and protecting assignment sequence *before and until* treatment begins. *Blinding* is concerned with protecting assignment sequence after allocation.

A possible limitation to any meta-analysis is that the trials may be so varied (heterogeneous) that producing a pooled effect is meaningless. In this meta-analysis, studies were heterogeneous in routes of administration, and types of glucosamine and chondroitin used. And outcomes were measured in different ways. Nevertheless, the investigators felt the effect sizes remained relatively constant suggesting that heterogeneity did not adversely affect the analysis.

Glucosamine and chondroitin have been widely publicized in the lay press.

This editorial presents several terms which we may find frequently mentioned in the literature: publication bias, funnel plots, nutraceuticals. However, almost all trials reported in the flagship journals which are supported by drug companies will cite that support.

What should the primary care clinician advise? I would not prescribe either. For those already self-prescribing the neutraceuticals and reporting benefit, I would not insist that they discontinue, unless future reports indicate toxicity or incompatibility with other drugs. RTJ

3-20 AMIODARONE TO PREVENT RECURRENCE OF ATRIAL FIBRILLATION.

Atrial fibrillation (**AF**) is a risk factor for embolic stroke and heart failure. Patients may have disabling palpitations and impaired cardiac performance due to loss of effective atrial contraction even after control of ventricular rate. Exercise tolerance may be reduced.

It is common practice to restore sinus rhythm. Prevention of recurrences of AF can improve cardiac function and relieve symptoms. However, AF recurs within 3 to 6 months in at least half of treated patients. Long-term use of quinidine and other class 1 agents has been questioned because of possible increased mortality. Concern about pro-arrhythmic effects is particularly pertinent for patients with AF because, by itself, AF is rarely fatal.

Amiodarone [*Cordarone; Pacerone*] in low doses has been suggested as an effective and safe agent to prevent recurrences of AF after sinus rhythm has been restored.

This study assessed the effect of *low-dose* amiodarone on preventing recurrences of AF.

Conclusion: Amiodarone was more effective than the beta-blocker sotalol and the anti-arrhythmic drug propafenone [*Rhythmol*] in maintaining sinus rhythm.

STUDY

1. Prospective multicenter trial randomized over 400 patients (mean age 65) to: 1) amiodarone, or 2) sotalol, or 3) propafenone in open label fashion.
2. All patients had at least one episode of AF within the previous 6 months. All who had AF lasting more than 48 hours prior to randomization received anticoagulation adjusted to achieve an INR of 2.0 or more for a minimum of 3 weeks before randomization.
3. Administered loading doses of the drugs (amiodarone 10 mg/kg daily for 14 days, then 300 mg per day for 4 weeks, and then a maintenance dose of 200 mg per day). Electrical cardioversion was performed (if necessary) within 21 days after randomization.
4. Mean daily dose of amiodarone = 327 mg at day 21; 205 mg at 3 months; and 186 mg at 12 months.
5. Primary end-point = length of time to a first recurrence of AF.

RESULTS

1. After a mean of 16 months follow-up: 65% of amiodarone patients remained in sinus rhythm vs 37% of those assigned to sotalol or propafenone.
2. Adverse effects requiring discontinuation of the drug: 18% in amiodarone groups vs 11% of sotalol-propafenone groups.
3. Overall 34% of amiodarone patients stopped taking the drug vs 46% in the other 2 groups. Reasons: lack

of efficacy (frequent recurrences of AF or need for repeated cardioversion) — 8% in amiodarone group vs 28% in placebo; non-compliant — 7% in each group; adverse effects 18% vs 11%. No episodes of ventricular tachycardia occurred in the amiodarone group

4. Adverse effects from amiodarone: GI events, insomnia, and fatigue. One patient was considered to have definite pulmonary toxicity. Two patients developed hypothyroidism; one, hyperthyroidism.

DISCUSSION

1. Amiodarone was more effective than sotalol or propafenone in maintenance of sinus rhythm in patients with AF. "The difference in efficacy we observed was striking." Amiodarone was about twice as effective as two other commonly used anti-arrhythmics.
2. Amiodarone warrants consideration as first- or second-line therapy in patients in whom maintenance of sinus rhythm is desired.
3. The rates of recurrence in patients taking quinidine and flecanide have been reported similar to those in this study taking sotalol or propafenone.
4. Amiodarone was generally well tolerated. Serious adverse events were uncommon. No pro-arrhythmic effect was observed.
5. The low dose (200 mg/d) of amiodarone probably accounted for the lower incidence of adverse effects. Long-term toxicity was not determined.
6. "We believe that our results challenge the notion that amiodarone should be used only in patients whose conditions are resistant to other drugs." "Amiodarone should be a drug of choice for patients with recurrent atrial fibrillation and structural heart disease, particularly those with left ventricular dysfunction."

CONCLUSION

Amiodarone was more effective than sotalol or propafenone for the prevention of recurrences of AF.

NEJM March 30, 2000; 342: 913-20 Original investigation by the Canadian Trial of Atrial Fibrillation Investigators, first author Denis Roy, Montreal Heart Institute, Canada.

Comment:

Is this a valid clinical point for primary care? Amiodarone is a "difficult" drug. (Read the PDR) It is indicated for life-threatening ventricular arrhythmias not responsive to other available anti-arrhythmics. Use should be restricted to physicians familiar with the drug. However, the dose in this study was lower than recommended maintenance doses for ventricular arrhythmias — thus, lowered toxicity. RTJ

3-21 NEW GUIDELINES FOR STROKE PUBLISHED

The Royal College of Physicians has prepared a national strategy for stroke. It covers all aspects of stroke care from diagnosis to rehabilitation. Stroke management is best undertaken by a specialized team. Strong evidence exists that patients treated in stroke units are less likely to die and more likely to recover fully or partially.

Recommendations for treatment of acute stroke:

Strongest evidence of efficacy (Grade A):

Aspirin 300 mg given as soon as possible unless hemorrhage is strongly suspected.

No other drug treatment should be given unless part of a randomized trial.

Thrombolytic treatment with tissue plasminogen activator (tPA) should be given only in a specialized center within 3 hours of the onset of stroke and only when hemorrhage has been definitely excluded.

When the stroke has caused weakness or paralysis of the legs, full length compression stockings should be applied to prevent venous thrombosis.

BMJ March 25, 2000; 320: 823 News from the MJ staff

Comment: The guidelines are available on the WWW. www.rcplondon.ac.uk/ceeu_stroke_home.htm

See also: Acute Ischemic Stroke *Extracts from "Clinical Evidence"* BMJ March 11, 2000; 320: 692-96

Beneficial:

Stroke units

Aspirin

Trade-off between benefits and harms:

Thrombolytic treatment

REFERENCE ARTICLE

3-22 SCABIES AND PEDICULOSIS

SCABIES

The article reviews etiology, epidemiology, clinical manifestations, diagnosis, and

Treatment:

Eight agents have been proposed as topical scabicides worldwide. The article concentrates on 2:

1) Permethrin (*Nix; Elimite; Acticin*): 5% cream is a first line drug because it has

excellent activity and low toxicity. It is at least as effective as lindane. The risk of toxic effects is at least 40 times lower than for 1% lindane lotion. It should be washed off after 12 hours.

2) Lindane (lotion and shampoo): A single 6 h application effectively treats scabies. Lindane-resistant scabies has been noted. Permethrin is effective in these cases. Safety is of some concern because of neurotoxicity. However, millions of patients have been treated successfully, and toxic effects resulted mainly from overdose, or abnormally high absorption from an altered cutaneous barrier. Low cost is an advantage.

Close contacts should be treated at the same time, whether or not symptoms are present. Application should be made over the entire body with particular attention to the groin, fingernails, toenails and behind the ears. Clothes and bedding must be decontaminated.

3) Ivermectin (*Stroectol*): an oral drug is an effective anti-parasite. A single dose of 100 to 200 mg can lead to cure 15 to 30 days later, even in HIV positive individuals. In severe cases, a repeat dose or two may be needed, separated by 1 to 2 weeks. The drug should help eradicate epidemic or endemic scabies, as in nursing homes. It is effective, safe, cheap, and convenient. But some features of drug management remain unclear. This probably explains why it has not been approved for use in scabies and head lice in the US.

PEDICULOSIS

The article discusses etiology, epidemiology, clinical manifestations, diagnosis, and

Treatment:

Head lice: many agents are available, many over the counter.

1) Malathion is an organophosphate which irreversibly inhibits cholinesterase. It is considered safe. However, the manufacturer withdrew it twice from the US market because of its commercial failure, probably caused by odor, flammability, and long application time. The FDA has approved 0.5% malathion in isopropanol and relaunched it partly to confront the emergence of resistance to other agents.

2) Permethrin is an effective drug. It is cosmetically acceptable. Adverse effects are local and mild. It can be a fire hazard. Application times are short.

3) Ivermectin , both oral and topical have been reported effective.

There is no clear consensus as to what defines the best treatment for eradication. But because of efficacy and safety, permethrin and malathion can be recommended. After treatment and a neutral shampoo, a fine-toothed comb may be used to remove nits.

Pubic lice:

Infestation requires treatment of patient and sexual partners. Measures are the same as for head lice. The hair of the head and beard, as well as axillary hair should be treated. .

Lancet March 4, 2000; 355: 819-26 "Seminar", review article by Oliver Chosidow Assistance Publique-Hopitaux de Paris, France.

REFERENCE ARTICLE

3-23 NON-INVASIVE METHODS OF ARTERIAL AND VENOUS ASSESSMENT

Diagnostic and therapeutic decisions in patients with vascular disease are guided primarily by history and the physical examination. Use of non-invasive investigations has increased significantly in the recent years. This concise review describes the main investigative techniques:

A. Principles of vascular ultrasonography (Doppler).

B. Investigation of arterial disease: ankle-brachial pressure index, diabetic limbs, walk test, duplex ultrasonographic scanning, identification of distal vessels for arterial bypass grafting, transcranial Doppler ultrasonography, helical or computed tomography, magnetic resonance angiography.

C. Investigation of venous disease: Venous ultrasonography to identify deep vein thrombosis, color duplex scanning for venous reflux.

BMJ March 11, 2000; 320: 698-701 "Clinical Review" first author Richard Donnelly, University of Nottingham, UK

Comment:

The review mentions one aspect of screening by ultrasound in patients with intermittent claudication which had escaped me before: the ankle-brachial pressure index will fall with exercise. Normally the index remains unchanged. See figure p 700 RTJ

REFERENCE ARTICLE

3-24 NEUROLOGICAL COMPLICATIONS OF THE REACTIVATION OF VARICELLA-ZOSTER VIRUS

Varicella-zoster (**VZ**) virus is a herpes virus which infects only humans. It causes chickenpox (varicella) and then becomes latent in cranial nerves and dorsal-root ganglia. It frequently reactivates years later and produces herpes zoster (shingles) and post herpetic neuralgia. It also at times produces disease in the central nervous system.

This article reviews progress and understanding of the neurological complications of re-activation of the virus. In addition to shingles and postherpetic neuralgia other complications of the CNS include myelitis, encephalitis, arteritis (both large and small), ventriculitis and meningitis. There are effective antiviral drugs. PCR analysis and antibody testing of cerebrospinal fluid to confirm the role of VZ should be used for diagnosis.

A form of reactivation in peripheral nerves can occur without the classical herpetic rash (zoster sine herpete). "Preherpetic neuralgia" is another unusual form in which the typical radicular pain precedes the shingles by days or weeks.

We await studies assessing a trial of varicella vaccine to boost immunity in middle age to prevent zoster.

Postherpetic neuralgia (**PHN**):

PHN is defined as pain that persists more than 6 weeks after development of the rash. Once it disappears, it does not recur. Age is the most important factor in predicting its occurrence. It does not occur before age 50, therefore immunocompetent young adults and children with zoster probably do not need antiviral therapy aimed at preventing PHN. After age 60, more than 40% of patients with zoster develop PHN. (*Up to 1/3 of elderly patients have PHN at 6 months. RTJ*) Controlled trials of oral antiviral drugs aimed at preventing PHN and continued for 6 months have not been shown to be effective in prevention. Nevertheless acyclovir or famcyclovir are given empirically to older patients with zoster for 7 to 10 days hoping for a benefit in prevention of PHN..

"Despite many trials, the optimal therapy for preventing postherpetic neuralgia has not been determined." Most studies have focused on antiviral drug and steroids, or both.

Once PHN has developed, there is no universally accepted treatment for the chronic pain. More than 40 pharmochologic, antiseptic, and surgical therapies have been tried with limited success. Tricyclic antidepressants (amitriptyline; nortriptyline) and anticonvulsants (carbamazepine; phenytoin) relieve pain in some patients. One anecdotal report described dramatic improvement with gabapentin. Some clinicians use a short course of corticosteroids (prednisone) to reduce inflammation that may be contributing to the pain..

NEJM March 2, 2000; 342: 635-45 "Medical Progress", review article, first author Donald H Gilden, University of Colorado Health Sciences Center, Denver.

Comment:

PHN is a great burden in the elderly. I was disappointed that this latest state-of-the-art review was no more optimistic about prevention and therapy. Regardless, clinicians must prescribe some form of therapy with as much enthusiasm and support as they can produce. I am not sure how successful our

colleagues in pain medicine are in controlling the discomfort. Fortunately in most patients the pain gradually wanes over a period of months, but may last for years.

That PHN spares the young and occurs only in the elderly is a fascinating clinical observation. If we knew why, some of the secrets of prevention of PHN might be revealed. I presume it is related to the degree of immunity. This would predict an effective preventive action against PHN by re-immunizing older persons with vaccine. It also raises the question about duration of immunity after vaccine is given in childhood. Will the immunity wane in persons who have not have had naturally acquired chickenpox and lead to in increased incidence of PHN in previously immunized individuals?

My latest "Clinical Evidence" (June 2000 pp 358-65) reviews the evidence:

A. Preventing PHN (treatment during the period of rash):

1) Antiviral agents (Acyclovir; Famcyclovir; Valaciclovir) taken daily (for 7 to 14 days) reduces the prevalence of PHN pain at 6 months. Adherence to treatment may be better with the newer drugs because of the reduced number of doses required.

2) Amitriptyline (*Elavil*, a tricyclic anti-depressant) 25 mg daily begun within 48 hours of onset of HZ and continued for 90 days reduced prevalence of PHN at 6 months.

3) Prednisone added to acyclovir produced short term benefit in relieving discomfort, but no significant reduction in PHN at 6 months.

B. Treating established PHN (after rash):

1) Tricyclic antidepressants given for 4 to 6 weeks are associated with pain relief at the end of the treatment period.

2) Narcotics (eg, oral oxycodone) provide pain relief. (One review stated that oral narcotics are underused in treatment of PHN.)

3) Gabapentin (an anti-convulsant) at the end of 8 weeks treatment was reported to reduce pain.

4) Lidocaine patches were associated with a short-term reduction in average pain scores. The reviewers consider effectiveness unknown.

Prevention and treatment of PHN is still unsatisfactory. Most clinicians will use all modalities including anti-virals, anti-depressants, and prednisone, hoping for the best, and hoping the individual patient will tolerate the side-effects. The earlier treatment is started, the more likely a beneficial effect. I would prescribe amitriptyline (*Elavil*) 25 mg daily for 3 months in addition to other drugs. RTJ

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