PREVENTION OF A FIRST STROKE
ANTIHYPERTENSIVE DRUGS IN VERY OLD PEOPLE:
SHOUL AGE AFFECT MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION?
IS INTENSIVE DRUG THERAPY APPROPRIATE FOR OLDER PATIENTS?
BEDTIME INSULIN REGIMENS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS
TREATING TYPE 2 DIABETES WITH RESPECT
CALCIUM-CHANNEL BLOCKADE IN OLDER PATIENTS WITH DIABETES AND ISH
THE EVIDENCE FOR BETA-BLOCKERS IN HEART FAILURE
HOW LONG TO CONTINUE ANTICOAGULATION IN IDIOPATHIC THROMBOEMBOLISM
TRAVELER’S DIARRHEA
HEARTBURN – A SERIOUS SYMPTOM
MEDICAL FUTILITY IN END-OF-LIFE CARE
THE RULE OF DOUBLE EFFECT
UNCLOAKING THE MENINGOCOCCUS
BUPROPION VS A NICOTINE PATCH FOR SMOKING CESSATION
FIBROMYALGIA — WHAT IS IT?
EVIDENCE AND ETHICS
EVIDENCE-BASED INTERVENTIONS AND COMPREHENSIVE TREATMENT
GLYCEMIC INDEX DETERMINES SERUM HDL-CHOLESTEROL CONCENTRATIONS
ARE THERE GOOD AND BAD CARBOHYDRATES FOR HDL CHOLESTEROL?
THE PHYSICAL CONSEQUENCES OF DEPRESSIVE ILLNESS
CHEMOPROPHYLAXIS FOR OCCUPATIONAL EXPOSURE TO HIV

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

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

A public service publication. Copies on file in Charlotte AHEC library.
3-1 PRIMARY PREVENTION OF STROKE: Consensus Statement

Members of the National Stroke Association Stroke Prevention Advisory Board present a consensus statement on primary prevention of stroke. This places, in one document, information of value to patients and a check list for physicians.

Six important stroke risk factors for a first stroke: hypertension; myocardial infarction (MI); atrial fibrillation; diabetes; blood lipids; and asymptomatic carotid stenosis.

Four lifestyle risk factors were also identified: cigarette smoking; alcohol overuse; limited physical activity; and adverse dietary habits.

The inclusion of asymptomatic carotid stenosis may be subject to debate since stroke and death may follow surgery in some patients.

3-2 3-3 TREATMENT OF HYPERTENSION AND MYOCARDIAL INFARCTION IN THE ELDERLY.

Francois Gueyffier, Claude Bernard Hospitals, Lyon France, and colleagues collected data in over 1500 patients over age 80 included in randomized trials. The incidence of non-fatal stroke was lower in the treated group. NNT(benefit-1 year) = 100). The incidence of major cardiovascular events was reduced from 39% to 22%. Although there was no significant reduction in death, the results indicate a reduction in illness and disability.

Khalid Barakat, Royal Hospitals NHS Trust, London, report in a prospective cohort study that patients with acute MI over age 69 were less likely to receive thrombolysis and beta-blockers. Older patients without heart failure had a better prognosis than younger patients with heart failure. Seventy percent of the elderly who survived to hospital discharge were still alive 3 years later.

An age limit beyond which treatment cannot be recommended cannot be justified. Treatment of hypertension and use of thrombolysis and beta-blockers in the very old must be individualized.

3-7 CALCIUM BLOCKERS FOR OLDER PATIENTS WITH ISOLATED SYSTOLIC HYPERTENSION

A study from the Systolic Hypertension in Europe Trial Investigators (first author Jaakko Tuomilehto, Helsinki, Finland) followed 4600 patients over age 60 for 2 years. The calcium blocker nitrendipine proved beneficial overall. It was especially beneficial in patients with diabetes and ISH in whom cardiovascular mortality was reduced by 76%; stroke by 73%. This does not support the hypothesis that long-acting calcium blockers are harmful.

3-8 ANTICOAGULATION FOR IDIOPATHIC VENOUS THROMBOEMBOLISM — How Long to Anticoagulate those with a First Episode

Clive Kearon, McMaster University, Hamilton Canada, and colleagues address this oft-asked question. They randomized 160 patients after the standard 3-months anticoagulation. The group in which anticoagulation
was continued for up to 10 months had far less recurrence (1% vs 20%) than the group in which it was discontinued after 3 months. They concluded that prolonged treatment is indicated. How long? — not determined.

**HIGHLIGHTS MARCH 1999**

3-1 PREVENTION OF A FIRST STROKE

This article identified six important stroke risk factors for a first stroke: hypertension; myocardial infarction (MI); atrial fibrillation; diabetes; blood lipids; and asymptomatic carotid stenosis.

Four lifestyle risk factors were also identified: cigarette smoking; alcohol use; physical activity; and diet.

Several interventions can reduce risk of a first stroke. JAMA March 24/31, 1999; 281: 1112-20

3-2 ANTIHYPERTENSIVE DRUGS IN VERY OLD PEOPLE: A Subgroup Meta-analysis of Randomised Controlled Trials

An age limit beyond which hypertension should not be treated cannot be justified. Lancet March 6, 1999; 353: 793-96

3-3 HOW SHOULD AGE AFFECT MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION?

Elderly patients with acute MI were treated less vigorously than younger patients. The prognosis was substantially influenced by left ventricular failure. Some elderly patients have better outlooks than younger patients with adverse clinical factors. Considering age independently of clinical status is inappropriate. Lancet March 20, 1999; 353: 955-59

3-4 IS INTENSIVE DRUG THERAPY APPROPRIATE FOR OLDER PATIENTS?

The evidence from clinical trials that included older patients, however, did not support restriction of beta-blockers or thrombolytic agents from the elderly. A statistical model has shown that thrombolysis administered to patients over age 75 was cost-effective. And beta-blocker use in elderly patients was associated with lower mortality at 2 years.

"Owing to the greater incidence of comorbid illness in the elderly, physicians will have to be especially diligent in screening older patients for treatment with thrombolysis, beta-blockers, and other agents." Lancet March 20, 1999; 353: 940

3-5 COMPARISON OF BEDTIME INSULIN REGIMENS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

A simple bedtime insulin regimen in patients whose type 2 diabetes was poorly controlled with sulfonylurea achieved better control. This was attributed to education and self-adjusting insulin dose. The combination of bedtime insulin and metformin gave the best results. Annals Int. Med. March 2,1999; 130: 389-96

3-6 TREATING TYPE 2 DIABETES WITH RESPECT

Intensive control of hypoglycemia can be achieved with relatively low risk of hypoglycemia or weight gain. Annals Int. Med. March 2, 1999; 120: 440-41

3-7 EFFECTS OF CALCIUM-CHANNEL BLOCKADE IN OLDER PATIENTS WITH DIABETES AND SYSTOLIC HYPERTENSION
Treatment of isolated systolic hypertension with the calcium-channel blocker, nitrendipine, was beneficial in older patients, especially in older patients with diabetes. These findings do not support the hypothesis that long acting calcium-channel blockers may be harmful in diabetic patients. NEJM March 4, 1999; 340: 67-84

3-8 THE EVIDENCE FOR BETA-BLOCKERS IN HEART FAILURE

Benefit of beta-blockers equals or Surpasses that for ACE inhibitors. Most patients in the trials of beta-blockers were already taking ACE inhibitors, so the benefits of beta-blockade appear additional to those of ACE inhibitors. "The evidence that beta-blockers reduce mortality in patients with left ventricular systolic dysfunction is now compelling."

They are most effectively and safely used in patients with milder symptoms to retard deterioration and increase the length and quality of life. BMJ March 27, 1999; 824-25

3-9 A COMPARISON OF THREE MONTHS OF ANTICOAGULATION WITH EXTENDED ANTICOAGULATION FOR A FIRST EPISODE OF IDIOPATHIC VENOUS THROMBOEMBOLISM

Patients with a first episode of idiopathic thromboembolism should be treated with anticoagulation for longer than 3 months. How long? – to be determined later. NEJM March 25, 1999; 340: 901-07

3-10 EPIDEMIOLOGY, ETIOLOGY, AND IMPACT OF TRAVELER’S DIARRHEA IN JAMAICA

The incidence of TD remains high. Travelers should avoid the known risk factors. JAMA March 3, 1999; 281: 811-17

3-11 HEARTBURN – A SERIOUS SYMPTOM

Heartburn is the hallmark of gastroesophageal reflux, a disorder that may lead to esophagitis, progressing to metaplastic columnar mucosal changes (Barrett’s esophagus), and ultimately to adenocarcinoma. Many patients with heartburn receive short-term treatment, which allows frequent relapses. "Physicians need to be aware that gastroesophageal reflux is a chronic disorder that usually calls for maintenance therapy." NEJM March 18, 1999; 340: 878-79

3-12 MEDICAL FUTILITY IN END-OF-LIFE CARE

The council finds great difficulty in assigning an absolute definition to the term futility since it is inherently a value-laden determination. A fair process approach is favored for determining and subsequently withholding or withdrawing what is felt to be futile care, without recourse to the court system. JAMA March 10, 1999; 281; 937-41

3-13 THE RULE OF DOUBLE EFFECT

The rule of double effect is the philosophical underpinning for the critically important concept of a side effect.

"Clinicians opposed to euthanasia and assisted suicide can understand that they might conscientiously use potent drugs to treat terminally ill patients under circumstances in which hastening the death of a patient can be considered a morally permissible side effect." Archives Int Med March 22, 1999; 159: 545-50

3-14 UNCLOAKING THE MENINGOCOCCUS: Dynamics of Carriage and Disease

"An increase in the incidence of meningococcal disease in the population is largely a reflection of the introduction, transmission, and acquisition of new meningococcal strains of a virulent clonal group or groups, the introduction of a large
number of susceptibles into a population with circulating virulent clonal groups, and factors (eg, close contact) that enhance transmission or invasion of these strains." Lancet March 20, 1999; 353: 941-42

3-15  A CONTROLLED TRIAL OF SUSTAINED-RELEASE BUPROPION, A NICOTINE PATCH, OR BOTH FOR SMOKING CESSATION
Treatment with bupropion alone, or in combination with nicotine patch, resulted in significantly higher rates of cessation at one year than either patch alone or placebo. NEJM March 4, 1999; 340: 685-91

3-16  FIBROMYALGIA FALLS FOUL OF A FALLACY
"Fibromyalgia, the neurasthenia of the late 20th century, is about to follow its 19th century namesake (neurasthenia), paying yet again the penalty of a failure to distinguish between cause and effect." Lancet March 27, 1999; 353: 1092-93

3-17  EVIDENCE AND ETHICS
"Evidence-based medicine and the clinical pathways derived from it can aid, but should never supercede or replace, the judgement of a clinician who knows both the patient and the evidence."
Lancet March 6, 1999; 353: 829-31

3-18  EVIDENCE-BASED INTERVENTIONS AND COMPREHENSIVE TREATMENT
"The complexity of clinical practice can be clarified by distinguishing the disease dimension from the personal dimension. In general practice, the personal dimension predominates. In general practice the personal dimension offers a particularly rich potential for intervention."
Lancet March 13, 1999; 353: 916-18

3-19  GLYCEMIC INDEX AS A DETERMINANT OF SERUM HDL-CHOLESTEROL CONCENTRATION
High glycemic index carbohydrate diets (increasing postprandial blood glucose concentrations) were associated with lower HDL-cholesterol concentrations; low glycemic index diets (lower postprandial blood glucose) with higher HDL-cholesterol concentrations.

The glycemic index was a stronger predictor of HDL-cholesterol concentrations than was dietary fat intake. Lancet March 27, 1999; 353: 1045-48

3-20  ARE THERE GOOD AND BAD CARBOHYDRATES FOR HDL CHOLESTEROL?
Diets low in fat necessarily have a high carbohydrate content. Low fat, high carbohydrate diets lower HDL-c (an adverse outcome) as well as LDL-c. Thus the recommendation to decrease fat and increase carbohydrate have come under scrutiny. The study suggests that not all carbohydrates lower HDL-c. Those with a low glycemic index may preserve HDL-c concentrations. Lancet March 27, 1999; 353: 1029-30

3-21  THE PHYSICAL CONSEQUENCES OF DEPRESSIVE ILLNESS
There is important and accumulating evidence that the physical consequences of depression are far from benign. In particular, increased risk of coronary artery disease and osteoporosis have received attention. The most consistent biologic abnormality in major depression is increased activation of the hypothalamic-pituitary-adrenal axis.
Depression is an illness with physical as well as social and psychological consequences. BMJ March 27, 1999; 318: 826

3-22 POSTEXPOSURE CHEMOPROPHYLAXIS FOR OCCUPATIONAL EXPOSURES TO THE HUMAN IMMUNODEFICIENCY VIRUS

This article considers: safety and efficacy of antiretroviral chemoprophylaxis and suggested clinical management. A table (p 934) presents the US Public Health Service recommendations for postexposure regimens. JAMA March 10, 1999; 281: 931-36

RECOMMENDED READING

3-16 FIBROMYALGIA FALLS FOUL OF A FALLACY
3-17 EVIDENCE AND ETHICS
3-18 EVIDENCE-BASED INTERVENTIONS AND COMPREHENSIVE TREATMENT

REFERENCE ARTICLES

3-1 PREVENTION OF A FIRST STROKE
3-12 MEDICAL FUTILITY IN END-OF-LIFE CARE
3-13 THE RULE OF DOUBLE EFFECT
3-22 POSTEXPOSURE CHEMOPROPHYLAXIS FOR OCCUPATIONAL EXPOSURES TO HIV

Reference Article -- Primary Prevention

3-1 PREVENTION OF A FIRST STROKE

A Review of Guidelines and a Multidisciplinary Consensus Statement from the National Stroke Association

"Although stroke remains a leading cause of death, disability, and health care expenditures, it can be prevented."

A consensus conference convened in April 1998 included attendees representing a range of disciplines. Evidence was based on a literature review. The objective of this statement is to establish, in a single resource, up-to-date recommendations for primary care physicians regarding prevention of a first stroke.

Six important stroke risk factors were identified: hypertension; myocardial infarction (MI); atrial fibrillation; diabetes; blood lipids; and asymptomatic carotid stenosis.

Four lifestyle risk factors were identified: cigarette smoking; alcohol use; physical activity; and diet.

Several interventions can reduce risk of a first stroke:

Good evidence for direct stroke reduction exists for: treatment of 1) hypertension; 2) warfarin for patients after MI who have atrial fibrillation, decreased left ventricular ejection fraction, or left ventricular thrombus; 3) "statin" drugs for patients after an MI; 4) warfarin for patients with atrial fibrillation and specific risk factors, and 5) carotid endarterectomy for stenosis over 60%.

Observational studies support the role of modifying life style-related risk factors: 1) smoking, 2) alcohol use, 3) physical activity, and 4) diet.

Hypertension:

Is the most prevalent and modifiable risk factor. Clinical trials establish that treatment does reduce risk of stroke. This includes treatment of isolated systolic hypertension in the elderly. Over half of strokes occur in persons over age 75. Treatment includes lifestyle changes as well as drugs (diuretics in particular).
Myocardial infarction:

Incidence of stroke in patients after MI is about 1% to 2% per year. Greatest risk is in the first month after MI. Warfarin is recommended to prevent stroke only if there are added risk factors: persistent atrial fibrillation, decreased left ventricular function, and left ventricular thrombi. Otherwise the risk is small and adverse effects of warfarin may outweigh benefits. Since aspirin is recommended routinely for prevention of recurrent MI, use for stroke prevention is automatic. After MI, "statin" drugs decrease risk of stroke in patients with normal to high lipid levels.

Non-valvular atrial fibrillation (AF):

Warfarin is indicated for non-valvular AF for patients with additional specific risk factors: age, (>75), previous TIA or stroke, hypertension, heart failure, and diabetes. Different studies identify different risk factors. Aspirin is recommended for those without risk factors. "Warfarin continues to remain underused for older persons."

Diabetes

Is a well-established risk factor for stroke. However, it is not conclusively determined that tight control of glucose reduces risk. Tight control of blood pressure in patients with hypertension (including isolated hypertension) and diabetes substantially reduces risk.

Asymptomatic carotid disease:

Treatment presupposes that patients have a reasonable life expectancy (> 5 years) and surgery can be performed with acceptable risk (perioperative morbidity-mortality < 3%). The degree of stenosis is the key determinant. Those with stenosis < 60% do not benefit. For stenosis 60-99% the absolute reduction in risk over 5 years is 6%, compared with medical treatment. But some guidelines do not support surgery for asymptomatic stenosis because of concern about reproducibility of the low surgical morbidity (< 1%) and the observation that surgery may not significantly reduce risk of major disabling stroke. Surgery cannot be recommended unless there is assurance that surgical risk is under 3%.

Lifestyle risks:

1. Cigarette smoking:

   Is an independent risk factor for ischemic stroke. (Relative risk = 1.5)

2. Alcohol use:

   A "J" shaped curve has been suggested for risk, with a protective effect of light consumption. High consumption increases risk.

3. Physical activity:

   Some benefit in lowering risk has been reported in whites, men, and younger adults. No dose-response has been shown consistently.

4. Diet:

   Decreased sodium intake (lowering BP), decreased saturated fat and cholesterol (lipid control), increased folic acid intake (lowering homocysteine levels), increased intake of fruits and vegetables, and weight control may be associated with decreased risk.

"Suboptimal control of risk factors continues to contribute to more than 700 000 strokes in the United States each year." Increasing adherence to reduction in risk factors is a major challenge.

"These recommendations should be applied and tailored to the individual patient."
Comment:

In the real world, surgery for asymptomatic carotid stenosis presents grave concerns. The absolute risk of stroke without surgery is low. Any clinician who recommends surgery for an asymptomatic patient, and then observes the patient stroked out will understand. RTJ

===========================================================================

3-2 ANTIHYPERTENSIVE DRUGS IN VERY OLD PEOPLE: A Subgroup Meta-analysis of Randomised Controlled Trials

Some authorities have suggested that treatment of hypertension in very old patients might not be effective, or even harmful.

This study collected data from subgroups of RCTs to assess evidence for or against antihypertensive treatment in people over age 80.

Conclusion: An age threshold beyond which hypertension should not be treated cannot be justified.

STUDY

1. Collected data from all participants age 80 and over in RCTs of antihypertensive drug treatment.
2. Almost 900 actively treated patients and almost 800 controls were included.
3. Primary outcome = fatal and non-fatal stroke.

RESULTS

1. Treatment was associated with 1 non-fatal stroke for about 100 patients treated each year.
   \[(\text{NNT}_{\text{benefit-1 year}}) = 100.\]
2. Rates of major cardiovascular events and heart failure were significantly decreased, by 22% and 39%.
3. No significant reduction in cardiovascular death or death from all causes.

DISCUSSION

1. The inconclusive findings for mortality contrast with the benefit for non-fatal events.
2. The positive results of the study were not robust, but do not suggest there is any age limit above which hypertension should not be treated.

CONCLUSION

An age limit beyond which hypertension should not be treated cannot be justified.

Lancet March 6, 1999; 353: 793-96 Original investigation, first author Francois Gueyffier, Claude Bernard University, Lyon Hospitals, France.

3-3 HOW SHOULD AGE AFFECT MANAGEMENT OF ACUTE MYOCARDIAL INFARCTION?
About 75% of patients with acute myocardial infarction are older than 70 years. Patients in this age group are commonly treated less vigorously than younger patients.

This study examined how age does and should affect the management of older patients.

Conclusion: Consideration of age independently of clinical status is inappropriate.

**STUDY**

1. Prospective cohort study entered over 1200 consecutive patients admitted with acute myocardial infarction (MI) to a general hospital; 270 were between age 70-79; 80 over 80.
2. Assessed the association between age and clinical variables.
3. End-point — death.

**RESULTS**

1. Patients 70 and older took longer to arrive at the hospital.
2. They were less likely to receive thrombolysis (odds ratio = 0.6) and be discharged on beta-blockers (odds ratio = 0.25) than patients younger than 60.
3. Left ventricular failure (HF) was the strongest independent predictor of death within 1 year. (Adjusted hazard ratio = 4.8)
4. Patients over age 69 who were without HF had significantly better survival than patients under age 60 who had HF.
5. 70% of the elderly patients who survived to hospital discharge were still alive 3 years later.
6. Independent predictors of death in 1 year:

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 60</td>
<td>1.0</td>
</tr>
<tr>
<td>60-69</td>
<td>1.3</td>
</tr>
<tr>
<td>&gt; 69</td>
<td>2.5</td>
</tr>
<tr>
<td>Sex Female</td>
<td>1.7</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.5</td>
</tr>
<tr>
<td>Q wave infarction</td>
<td>1.8</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>4.8</td>
</tr>
</tbody>
</table>

**DISCUSSION**

1. Thrombolysis and beta-blockers were used less frequently in the elderly. (Certainly, contraindications are more common in the elderly.)
2. Older patients took longer to reach the hospital probably because of a lower level of urgency. Most however, reached within 12 hours. (The investigators’ protocol gives leeway to use of thrombolysis for those who have continuing pain with ST elevation after 12 hours.
3. "Age alone is unhelpful in defining risk and guiding management strategies."
4. Not all elderly patients have a poor outlook, and in the absence of left-ventricular failure, the outcome is often good.

**CONCLUSION**
Elderly patients with acute MI were treated less vigorously than younger patients. The prognosis was substantially influenced by left ventricular failure. Some elderly patients have better outlooks than younger patients with adverse clinical factors. Considering age independently of clinical status is inappropriate.


3-4 IS INTENSIVE DRUG THERAPY APPROPRIATE FOR OLDER PATIENTS?

Any explanation as to why therapy is restricted in elderly patients with myocardial infarction (MI) is likely to be complex and multifactorial.

Adverse drug reactions increase with age. In the Gusto trial of streptokinase in MI, incidence of stroke and bleeding complications increased by a factor of 2 to 3 in patients over age 75.

"The fear of iatrogenic stroke probably exerts a very powerful emotional influence on many physicians, and limits the extension of thrombolytic therapy to older patients."

The exclusion of elderly patients from clinical trials also contributes to delay in use of some medications and procedures in clinical practice.

The evidence from clinical trials that included older patients, however, did not support restriction of beta-blockers or thrombolytic agents from the elderly. A statistical model has shown that thrombolysis administered to patients over age 75 was cost-effective. And beta-blocker use in elderly patients was associated with lower mortality at 2 years.

"Owing to the greater incidence of comorbid illness in the elderly, physicians will have to be especially diligent in screening older patients for treatment with thrombolysis, beta-blockers, and other agents."

Lancet March 20, 1999; 353: 940  "Commentary", editorial by Steven B Gollub, Kansas University School of Medicine, Kansas City

Comment:

Thrombolysis in the elderly is another example of dilemmas facing primary care physicians. We cannot divine the prognosis of elderly patients with MI who do not receive thrombolysis. Some may survive, some will not. However, if thrombolysis leads to hemorrhagic stroke, patients and their families will likely blame the therapy. And the clinician will with certainty blame himself and the therapy. One may argue that giving the patient full information on which to base her consent will lessen the physician’s responsibility for adverse outcomes. But, how to fully inform a critically ill and distraught patient within a limited time frame? As usual, clinical judgement is the determinant.  RTJ

3-5 COMPARISON OF BEDTIME INSULIN REGIMENS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

A common clinical problem occurs when diabetes is poorly controlled by oral therapy. How should we then proceed?

This study compared different bedtime insulin regimens to evaluate effects on weight gain, hypoglycemic episodes, and glycemic control in patients inadequately controlled by oral therapy alone.

Conclusion: Bedtime insulin + metformin was the best regimen.
STUDY
1. Randomized, controlled trial entered 96 patients (mean age 58) with type 2 diabetes. All were poorly controlled with sulfonylurea therapy alone (mean HbA1c = 9.9%; mean fasting blood glucose = 214 mg/dL).
2. Randomized for 1 year:
   A. All received bedtime intermediate-acting insulin (neutral human isophane insulin)
   B. 1) Plus glyburide, 2) plus metformin, 3) plus glyburide and metformin, or 4) a second injection of the same insulin in the morning.
3. Measured body weight, biochemical and symptomatic hypoglycemia, and fasting glucose levels (by home measurement).
4. Insulin dose was self-adjusted according to the fasting glucose level:
   A. Starting at a dose in units equal to the fasting glucose measured in mmol/L.
      [Eg, if fasting glucose was 10 mmol/L (180 mg/dL), the starting dose was 10 units at bedtime.]
   B. Continuing doses—if the fasting glucose exceeded 8 mmol/L (140) on 3 consecutive measurements, the bedtime dose was increased by 4 units. If between 6 and 8 mmol/L (108 to 140) the dose was increased by 2 units.
5. The goal was to decrease the fasting glucose to less than 6 mmol/L (108 mg/dL). This was predicted to lower the HbA1c to less than 7.5%
6. Doses of the oral drugs remained the same. (See text)

RESULTS
1. At 12 months the mean dose of insulin in the metformin group was 39 units vs 20 to 24 in the other groups.
2. Body weight at 1 year, 1) metformin group – increased a mean of 0.9 kg; 2) the 3 other groups – increased by 3.6 to 4.6 kg.
3. The HbA1c decreased from 9.7% to 7.2% in the metformin group, significantly more than in the other groups.
4. Hypoglycemic episodes (symptomatic) occurred less frequently in the metformin group -- 1.8 during 12 months vs 3.3 to 3.9 in the other groups despite a higher dose of insulin.
5. Of 96 patients randomized, 88 (92%) completed the year trial. Drop outs included four patients taking metformin (10%) who developed side effects considered due to the drug (diarrhea, metallic taste, abdominal discomfort, rash).

DISCUSSION
1. Better maintenance of glycemic control in all groups was attributed to the education they received and teaching the patients to self-adjust insulin.
2. The group taking metformin + insulin had better outcomes than those taking metformin + glyburide (in addition to insulin). (Note that the former group took considerably more insulin.)
3. The absence of weight gain and the lower frequency of hypoglycemia were important benefits of metformin.
CONCLUSION

A simple bedtime insulin regimen in patients whose type 2 diabetes was poorly controlled with sulfonylurea achieved better control. This was attributed to education and self-adjusting insulin dose. The combination of bedtime insulin and metformin gave the best results.

Annals Int. Med. March 2, 1999; 130: 389-96 Original investigation, first author Hannele Yki-Jarvinen, University of Helsinki, Finland.

Comment:

Metformin is becoming more popular for initial therapy or added to insulin. RTJ

3-6 TREATING TYPE 2 DIABETES WITH RESPECT

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

“We have finally awakened to the fact that type 2 diabetes, whose very designation suggests second-class citizenship, is actually the predominant form of diabetes.” It is one of the most chronic severe diseases in the world, affecting an estimated 12% of the adult population in the US aged 40-74. It is a major cause of kidney disease, vision loss, and amputation.

In addition to the micro-vascular complications (nephropathy, retinopathy, and neuropathy) diabetes is accompanied by a 2-fold to 5-fold increase in macro-vascular disease. Most patients with type 2 diabetes are obese, and have dyslipidemia and hypertension. Cardiovascular disease accounts for as much as 75% of the mortality among patients with the disease.

Intensive glucose control clearly benefits the micro-vascular complications, but not the macro-vascular complications.

Worsening of metabolic control occurs inexorably over time in patients with type 2 diabetes. Whether the insulin-metformin regimen will spare patients this decline in control remains to be shown.

Intensive control of hypoglycemia can be achieved with relatively low risk of hypoglycemia or weight gain.

Annals Int. Med. March 2, 1999; 120: 440-41 Editorial by David M Nathan, Massachusetts General Hospital, Boston.

3-7 EFFECTS OF CALCIUM-CHANNEL BLOCKADE IN OLDER PATIENTS WITH DIABETES AND SYSTOLIC HYPERTENSION

In 1995, a meta-analysis suggested that short-acting calcium-channel blockers (CCBs) may provoke, rather than prevent myocardial infarction. Subsequently, commentaries have suggested that long-acting CCBs, including second generation dihydropyridines (amlodipine [Norvasc; Lotrel]; nisoldipine [Sular] may also be harmful, particularly in patients with hypertension and diabetes.

The Systolic Hypertension in Europe (Syst-Eur) trial1,2 recently reported that antihypertensive treatment initiated with the dihydropyridine nitrendipine reduced risk of stroke and cardiovascular events in older patients with isolated systolic hypertension (ISH).

The present study, a post hoc analysis of data in the Syst-Eur trial, was designed to determine effect of nitrendipine on long-term outcome in both diabetic and non-diabetic patients with ISH.
Conclusion: Nitrendipine-based antihypertensive therapy was particularly beneficial in older patients with diabetes and ISH.

STUDY
1. Entered over 4600 patients over age 60 (10% with diabetes) who had isolated systolic hypertension (systolic BP 160 to 219, and diastolic BP under 95).
2. Randomized, double-blind to: 1) active treatment with nitrendipine 10 to 40 mg daily with possible addition of enalapril and hydrochlorothiazide titrated to reduce systolic BP to less than 150, or 2) placebos.
3. Follow-up = 2 years.

RESULTS
1. Outcome (events per 1000 patient-years — non-diabetics:

<table>
<thead>
<tr>
<th></th>
<th>Treated (n = 2146)</th>
<th>Placebo (n = 2057)</th>
<th>NNT(benefit 1-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP Lower by 10.3/4.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality overall</td>
<td>19.8</td>
<td>21.6</td>
<td>555</td>
</tr>
<tr>
<td>Mortality cardiovascular</td>
<td>10.0</td>
<td>11.9</td>
<td>526</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>23.5</td>
<td>31.4</td>
<td>126</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.5</td>
<td>12.3</td>
<td>222</td>
</tr>
</tbody>
</table>

2. Outcome at 1 year per 1000 patients — diabetic:

<table>
<thead>
<tr>
<th></th>
<th>Treated (n = 252)</th>
<th>Placebo (n = 240)</th>
<th>NNT(benefit 1-year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP Lower by 8.6/3.9</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality overall</td>
<td>26.4</td>
<td>45.1</td>
<td>53</td>
</tr>
<tr>
<td>Mortality cardiovascular</td>
<td>8.3</td>
<td>27.8</td>
<td>51</td>
</tr>
<tr>
<td>All cardiovascular events</td>
<td>22.0</td>
<td>57.6</td>
<td>28</td>
</tr>
<tr>
<td>Stroke</td>
<td>8.3</td>
<td>26.6</td>
<td>54</td>
</tr>
</tbody>
</table>

3. Among diabetic patients, active treatment reduced cardiovascular mortality by 76%; stroke by 73%.
4. Among non-diabetics all cardiovascular events were reduced by 26% and stroke by 38%.
5. Benefit was much greater in patients with diabetics.

DISCUSSION
1. Treatment of isolated systolic hypertension beginning with a dihydropyridine calcium-channel blocker was beneficial in non-diabetic patients, and more beneficial in diabetic patients.
2. The cardiovascular benefit was the same whether patients continued to receive nitrendipine alone, or whether they subsequently received ACE inhibitor or diuretic.
3. In terms of absolute benefit, results suggest that treatment for 5 years would prevent 178 major cardiovascular events in every 1000 diabetic patients treated and in 39 in non-diabetic patients.
CONCLUSION

Treatment of isolated systolic hypertension with the calcium-channel blocker, nitrendipine, was beneficial in older patients, especially in older patients with diabetes. These findings do not support the hypothesis that long acting calcium-channel blockers may be harmful in diabetic patients.

NEJM March 4, 1999; 340: 67-84  Original investigation, first author Jaakko Tuomilehto, National Public Health Institute, Helsinki, Finland for the Systolic Hypertension in Europe Trial Investigators.

1. "Randomised Double-blind Comparison of Placebo and Active Treatment of Older Patients with Isolated Systolic Hypertension"  Lancet 1997; 350: 757-64
3. My calculations  RTJ

Comment:

This re-emphasizes several important points:

A. Isolated systolic hypertension should be treated.
B. Calcium blockers are safe and effective treatment. They may be the drug of first choice for ISH.
C. Lowering BP in diabetic patients with ISH is especially beneficial.

Other trials report treating BP in hypertensive diabetic patients to a lower level than non-diabetics yields increased benefits. The HOT trial1 reported that tighter control of BP (a target of 80 mmHg diastolic vs a target of 90) halved the risk of major cardiovascular events.


3-8  THE EVIDENCE FOR BETA-BLOCKERS IN HEART FAILURE

Equals or Surpasses that for Angiotensin Converting Enzyme Inhibitors

"Despite the evidence that ACE inhibitors improve the morbidity and mortality of heart failure (HF) secondary to left ventricular systolic dysfunction, the prognosis of heart failure (HF) has improved little over the past 30 years."

Now evidence is accumulating that beta-blockers, used in addition to ACE inhibitors, reduce mortality in HF.

There are now 25 trials that have randomized patients with HF to beta-blocker or control. Overall beta-blocker reduced odds of death by 36% (CI 25% to 45%). There was no evidence of heterogeneity between trial results and no evidence of publication bias.

By comparison, ACE inhibitors were associated with a 24% (CI 13% to 33%) reduction in odds of death in 39 trials in patients with HF.

Most patients in the trials of beta-blockers were already taking ACE inhibitors, so the benefits of beta-blockade appear additional to those of ACE inhibitors.
The editorialists calculate the best available evidence for the effect of combined therapy on reduction in mortality over 1 year – 1% reduction for ACE inhibitors alone; 3% for beta-blockers alone; and 5% for the combined therapy. (NNT benefit-1year = 20)

"The evidence that beta-blockers reduce mortality in patients with left ventricular systolic dysfunction is now compelling."

They are most effectively and safely used in patients with milder symptoms to retard deterioration and increase the length and quality of life.

They should be started in low doses and slowly titrated over weeks or months before attaining maintenance doses. Start low and go slow.

BMJ March 27, 1999; 324-25 Editorial, first author John G F Cleland, Castle Hill Hospital, Cottingham, Hull, UK.

3-9 A COMPARISON OF THREE MONTHS OF ANTICOAGULATION WITH EXTENDED ANTICOAGULATION FOR A FIRST EPISODE OF IDIOPATHIC VENOUS THROMBOEMBOLISM

Acute venous thromboembolism is usually treated with a short course (5-7 days) of heparin and a 3-month course of warfarin.

Previous analyses have suggested that, after anticoagulation is stopped, the risk of recurrent thromboembolism is greater in patients 1) who have persistent risk factors for thrombosis, and 2) whose initial episode of thrombosis occurred in the absence of apparent risk factors. Those in whom thrombosis develops in association with a transient risk factor such as surgery are less predisposed to recurrence.

These investigators hypothesized that patients with a first episode of idiopathic venous thromboembolism would benefit from a course of anticoagulation longer than 3 months.

Conclusion: An anticoagulation period longer than 3 months was more beneficial.

STUDY

1. Double blind study entered 162 patients who had a first episode of idiopathic venous thromboembolism.
   All had completed a 3-month course of anticoagulation.
2. Randomized to: 1) continuing warfarin with dose adjusted to an INR of 2.0 to 3.0, or 2) placebo.
3. Planned follow-up = 2 years to determine rates of recurrent symptomatic thromboembolism and bleeding.

RESULTS:

1. The trial was terminated at an average of 10 months because of efficacy of continued anticoagulation.
2. Twenty percent of patients assigned to placebo had recurrent thrombosis during follow-up (one fatal pulmonary embolus) vs 1.3 percent (only 1 patient who had discontinued warfarin months before) of those assigned to warfarin.
3. Three patients (4%) taking warfarin had non-fatal major bleeding vs none in the placebo group.

DISCUSSION
1. Those with known risk factors were excluded from this trial (ie, considered not to be idiopathic). This included fracture or plaster cast; hospitalization with bed rest for 3 or more consecutive days; use of general anesthesia; cancer; and known deficiency of antithrombin, protein C, or protein S.

2. Patients with a first episode of idiopathic thromboembolism have a high rate of recurrence which extends after a 3-month course of anticoagulation.

3. Extended warfarin therapy was effective in reducing rate of recurrence.

4. Anticoagulation was associated with risk of bleeding, but the benefits outweighed the risk.

5. Laboratory tests were performed on many patients entered. Factor V Leiden was not a clinically important risk factor for recurrence of "idiopathic" disease. Those with lupus anticoagulant were at increased risk. In this group, prolonged anticoagulation is particularly useful.

6. The study did not indicate how long anticoagulation should be continued.

7. "There is evidence that oral anticoagulation at a lower intensity (ie, with a target INR of less than 2.0) is effective in preventing venous thromboembolism, particularly when used for primary prophylaxis."

CONCLUSION

Patients with a first episode of idiopathic thromboembolism should be treated with anticoagulation for longer than 3 months. How long? – to be determined later.

NEJM March 25, 1999; 340: 901-07

Original investigation, first author Clive Kearon, McMaster University, Hamilton, Ontario, Canada

An editorial in this issue of NEJM (pp 955-56) comments:

What about patients with identifiable and reversible risk factors for thromboembolism? (Eg, surgery, trauma, immobilization). Current data suggest that a 6-week course of anticoagulation is sufficient, once the risk factor is removed.

The preceding study continues the approach to treating idiopathic thromboembolism as a chronic disease.

Risk of bleeding will be higher in primary care practice than in trials in which monitoring is done by specialists or a centralized facility. To improve the benefit/harm-cost ratio, a lower intensity of warfarin therapy could prove to be effective.

Other studies followed patients with idiopathic disease for up to 8 years. Incidence of recurrence rose with the years – 17% at 2 years; 25% at 5 and 30% at 8. Thus risk of recurrence lasts for years. Systemic hypercoagulability contributes to risk. About half of recurrent episodes occurred in the contralateral extremity. (Ie, many cases are not "idiopathic". A basic inheritable hypercoagulable state can be found in about half of the patients.)

Long-term anticoagulation (continued indefinitely) after an initial episode of venous thromboembolism should be considered, particularly for patients with persistent risk factors (cancer, antiphospholipid-antibody syndrome). Also for patients who have had more than one episode of idiopathic thromboembolism. "It is conceivable that nearly all patients with venous thromboembolism will eventually prove to have a genetic predisposition to the condition."

Patients with apparently idiopathic thrombosis are likely to be vulnerable to recurrent events initiated by repeated, clinically occult stimuli.

Comment:

The list of "idiopathic" VTE is shrinking. More acquired and genetic defects leading to a thrombotic tendency are being described. RTJ
Traveler’s diarrhea (TD) is a self-limited illness that usually resolves spontaneously within a few days. It has the potential to wreck a meticulously planned vacation.

This study assessed epidemiology and etiology of TD in Jamaica.

Conclusion: TD was common and disturbing. Better preventive measures are needed.

**STUDY**

2. Over 30,000 short-term visitors to the Montego Bay area of Jamaica completed a questionnaire before boarding a homebound flight.
3. Cultured stools of over 300 subjects who had TD.
4. Assessed incidence rates of 1) reported diarrhea and 2) classically defined TD ($\geq 3$ unformed stools in 24 hours with $\geq 1$ accompanying symptoms).
5. Assessed incapacity, risk factors, and etiology.

**RESULTS**

1. Attack rate for diarrhea was 23% overall. 12% had classical TD.
2. Onset of symptoms was at a mean of 4 days. Duration increased with severity of symptoms. Almost half of those with classical TD were incapacitated a mean of 12 hours.
3. Most tourists chose an all-inclusive travel package (food and beverage with hotel). This group had a significantly higher TD rate than those with other plans.
4. Tourists who stayed with friends or family had significantly lower TD rates.
5. The great majority had ice cubes in drinks; ate salads, dairy products; tap water; ice cream; hamburgers; and incompletely cooked chicken, lobster, or shrimp.
6. Fewer than 3% reported avoiding all potentially contaminated foods.
7. Only 2% used prophylactic medication, usually bismuth subsalicylate (Peptobismol).
8. There was a significant seasonal variation in total TD rates — 26% in May-October, and 15%-20% in December-May.
9. Some hotels had a consistently low attack rate; some a consistently high rate.
10. The most frequent pathogens — enterotoxigenic E coli, Rotavirus, and salmonella species. For most, no pathogen was determined. The cause of TD remains elusive in many patients.

**DISCUSSION**

1. Similar incidence rates have been reported by other studies.
2. Teenagers and young adults had a higher risk for the same length of stay, possibly due to their greater appetite and consequently higher intake of pathogens.
3. Honeymooners, irrespective of age, also had a higher risk, possibly associated with more elaborate and less hygienic buffets related to the ceremonies.
4. Lunch may be of a particularly high risk, since buffets are exposed for longer periods to higher ambient temperatures.
5. Travelers need a realistic plan to reduce TD — following restrictive dietary rules and avoiding potentially contaminated foods.
6. Hosts need a program of improved food hygiene.
7. Vaccines are in the offing.

CONCLUSION
The incidence of TD remains high. Travelers should avoid the known risk factors.

JAMA March 3, 1999; 281: 811-17 Original investigation, first author Robert Steffen, University of Zurich, Switzerland.

Comment:
The authors commend the Ministry of Health of Jamaica and Ministry of Tourism for their support of this forthright study. Oral vaccines targeted against td may soon be marketed against e coli, rotavirus. RTJ

3-11 HEARTBURN — A SERIOUS SYMPTOM
Heartburn is the hallmark of gastroesophageal reflux, a disorder that may lead to esophagitis, progressing to metaplastic columnar mucosal changes (Barrett’s esophagus), and ultimately to adenocarcinoma.
"Since the 1970s, the incidence of adenocarcinoma of the esophagus and gastric cardia has risen more rapidly than the incidence of any other cancer in the United States." There has been little change in incidence of squamous-cell carcinoma.
The metaplastic change of Barrett’s esophagus has features resembling the intestinal mucosa. It develops during re-epithelialization of the esophagus in an acid environment. The tissue can undergo dysplastic changes and eventually lead to adenocarcinoma.
About 20% of adults in the US have heartburn on a weekly basis. Severity and chronicity are difficult to quantify and cannot be used as a simple measure of mucosal injury. The only diagnostic study of value is endoscopy with biopsy. "Although a precise algorithm for the use of endoscopy with biopsy cannot be recommended, we believe that early assessment of the esophageal mucosa is warranted for any patient in whom heartburn is severe enough to be the primary symptom for which medical evaluation is sought."
Many patients with heartburn receive short-term treatment, which allows frequent relapses. "Physicians need to be aware that gastroesophageal reflux is a chronic disorder that usually calls for maintenance therapy."

NEJM March 18, 1999; 340: 878-79 Editorial by Sidney Cohen, and Henry P Parkman, Temple University School of Medicine, Philadelphia, PA
See also "Symptomatic Gastroesophageal Reflux as a Risk Factor for Esophageal Adenocarcinoma" NEJM March 18, 1999; 340: 835-31 "There is a strong and probably causal relation between gastroesophageal reflux and esophageal adenocarcinoma. The more frequent, more severe, and longer-lasting the symptoms, the greater the risk."

REFERENCE ARTICLE
3-12 MEDICAL FUTILITY IN END-OF-LIFE CARE
This article recommends a process-based approach to futility determinations. It includes steps aimed at deliberation and resolution including all involved parties, aimed at securing alternatives in the case of irreconcilable differences, and a final step aimed at closure when all alternatives have been exhausted.

"Use of life-sustaining or invasive interventions in patients in a persistent vegetative state or who are terminally ill may only prolong the dying process. What constitutes futile intervention remains a point of controversy. In clinical practice, controversy arises when the patient or proxy and the physician have discrepant values or goals of care. Since definitions of futile care are value laden, universal consensus on futile care is unlikely to be achieved."

The council finds great difficulty in assigning an absolute definition to the term futility since it is inherently a value-laden determination. A fair process approach is favored for determining and subsequently withholding or withdrawing what is felt to be futile care, without recourse to the court system.

JAMA March 10, 1999; 281; 937-41  Report of the Council on Ethical and Judicial Affairs, American Medical Association  
Comment: Clinicians should be ever mindful of cultural differences in attitudes for terminal care  RTJ

---

REFERENCE ARTICLE

3-13  THE RULE OF DOUBLE EFFECT

"The traditional rule of double effect specifies that an action with 2 possible effects, one good and one bad, is morally permitted if the action: (1) is not in itself immoral; (2) is undertaken with the intention of achieving the possible good effect, without intending the possible bad effect even if it may be foreseen, (3) does not bring about the possible good effect by means of the possible bad effect, and (4) is undertaken for a proportionately grave reason."

"We are only arguing that if one believes, for whatever reasons, that euthanasia and assisted suicide are always morally wrong, even if requested by a patient, then the rule of double effect can be used sensibly and coherently to examine important cases in the practice of medicine, particularly the care of dying."

The rule of double effect is the philosophical underpinning for the critically important concept of a side effect. "Clinicians opposed to euthanasia and assisted suicide can understand that they might conscientiously use potent drugs to treat terminally ill patients under circumstances in which hastening the death of a patient can be considered a morally permissible side effect."

Archives Int Med March 22, 1999; 159: 545-50 "Commentary", first author Daniel P Sulmasy, The John J Conley Department of Ethics, St. Vincents Hospital and Medical Center, New York  
Comment: I stumble over "always". All of us can imagine circumstances where we might shoot a loved-one to prevent needless torture. I also stumble over "intent".

---

3-14  UNCLOAKING THE MENINGOCOCCUS: Dynamics of Carriage and Disease

The human upper respiratory tract is the main reservoir of carriage and the site of Neisseria meningitidis dissemination. The dynamics of carriage and the relation between carriage and invasive meningococcal disease remain shrouded.
"By conservative estimate, 500 million out of the six billion people in the world carry N meningitidis in the nasopharynx. The highest rate of carriage is in adolescents and young adults. Carriage may last months in some, is intermittent in some, and transient or infrequent in some. Rates of transmission are much higher among populations living in confined areas (military recruits; dormitories). They are exacerbated by cigarette smoking and upper respiratory infections. However, the rates of carriage have not been especially useful in predicting outbreaks of disease.

Carriage is an immunizing process which results in protective antibody responses. Compared with the prevalence of carriage, disease is uncommon, largely because most N meningitidis isolated from the nasopharynx of carriers have limited pathogenic potential. Most epidemic and endemic cases of disease are caused by strains of a limited number of genetically defined clonal groups. Some groups are characterized by high rates of disease following nasopharyngeal acquisition, especially when first introduced into a population. Clonal groups found in the nasopharynx of symptom-free carriers (who are not case contacts) rarely cause disease, even in settings of high rates of transmission and acquisition.

"An increase in the incidence of meningococcal disease in the population is largely a reflection of the introduction, transmission, and acquisition of new meningococcal strains of a virulent clonal group or groups, the introduction of a large number of susceptibles into a population with circulating virulent clonal groups, and factors (eg, close contact) that enhance transmission or invasion of these strains."

Eradication of all meningococci is not likely or desirable. Control of transmission or prevention of meningococcal disease due to strains of virulent clonal groups would eliminate epidemic outbreaks and up to 75% of cases of endemic disease. Apart from the immediate chemoprophylaxis of close contacts to prevent secondary cases, identification of carriers of virulent clonal groups by sensitive molecular-based approaches and selective eradication of carriage by chemoprophylaxis should be considered as a strategy for reducing meningococcal disease in a community.

However, the key to effective control is immunoprophylaxis. Existing vaccines provide short-lived protection for only some segments of the population, and overall have a marginal effect on carriage rates or acquisition of carriage. It is not surprising that vaccines have a limited role in control of disease. New vaccines are being developed.

Lancet March 20, 1999; 353: 941-42  Editorial by David S Stephens, Emory University School of Medicine, Atlanta, GA

3-15 A CONTROLLED TRIAL OF SUSTAINED-RELEASE BUPROPION, A NICOTINE PATCH, OR BOTH FOR SMOKING CESSATION

Most smokers who quit with the aid of nicotine replacement therapy eventually start smoking again. Affect or mood appears to exert potent effects on the motivation to quit. Population-based studies report that smokers are more likely to have symptoms of affective disorders than non-smokers. Symptoms of nicotine dependence correlate with the magnitude of symptoms of depression.

Antidepressants and anxiolytics may be effective cessation aids.

This study was compared bupropion alone, bupropion + nicotine patch, nicotine patch alone, and placebo as aids to cessation.

Conclusion: Bupropion [Zyban], alone or combined with patch resulted in higher long-term cessation.

STUDY

1. Randomized, double-blind, placebo-controlled trial entered 900 smokers. All were volunteers motivated to quit.
2. None had clinical depression.
3. Treated for 9 weeks with: 1) sustained-release bupropion alone; 2) nicotine patch alone; 3) both bupropion and patch; or 4) placebos.
4. Follow-up = 1 year.

RESULTS

1. At 1 year: Bupropion alone Nicotine patch alone Both Placebos.
   Abstinence rates 30.3% 16.4% 35.5% 15.6%

2. Subjects in the combined group gained less weight than the others.
3. Over 1/3 of the subjects discontinued treatment with one or both medications.

DISCUSSION

1. Bupropion alone, or combined with a nicotine patch resulted in higher 1-year abstinence rates.
2. Combined bupropion-nicotine patch was not significantly better than bupropion alone.
3. All 3 treatments resulted in less severe withdrawal symptoms than placebo alone.
4. Withdrawals because of adverse effects: Placebo — 4%; patch — 7%; bupropion groups — 12%
5. Another 20% dropped out for reasons other than adverse effects.

CONCLUSION

Treatment with bupropion alone, or in combination with nicotine patch, resulted in significantly higher rates of cessation at one year than either patch alone or placebo.

NEJM March 4, 1999; 340: 685-91  Original investigation, first author Douglas E Jorenby, University of Wisconsin Medical School, Madison
Comment:

Attaining a 30% cessation rate is a significant accomplishment. Results will be less impressive in the "real world" of primary care. I believe bupropion can add to cessation rates in smokers who are strongly motivated to quit. The patch did not significantly increase quit rates compared with bupropion alone. Would adding a nicotine inhaler to bupropion increase quit rates?
The study was supported by Glaxco Wellcome. RTJ

Recommended Reading

3-16  FIBROMYALGIA FALLS FOUL OF A FALLACY

Fibromyalgia as a diagnosis was first conceived in 1981 to label a syndrome characterized by widespread pain and increased sensitivity to pressure at various "tender points". Subsequently, the spectrum of fibromyalgia was expanded to include clinical features such as fatigue, sleep disturbance, headache, and irritable bowel.

In 1990 the American College of Rheumatology announced classification criteria to distinguish it from other rheumatic conditions.
These commentators argue that these criteria were developed out of circular reasoning. "Fibromyalgia has become a proposition so broad that it includes all possibilities." The label is entrenched. But, it is so easily abused as to have become meaningless.

Fibromyalgia has been promoted as "a common and recognizable cause of chronic, diffuse musculoskeletal pain. This violates the dictum in logic that an effect — in this case an illness — should not be confused with its own cause. "Fibromyalgia cannot be both a state of musculoskeletal pain and the cause of that state."

Is the label "fibromyalgia" intended to imply the existence of a specific entity (an essentialist interpretation) or to be used only as a working hypothesis which groups certain clinical features together to test a hypothesis of causation (nominalist interpretation) ?

"The acceptance of fibromyalgia as an essentialist truth rather than a nominalist hypothesis has confounded scientific understanding of the phenomenon it purports to describe."

Proponents of fibromyalgia seek to diagnose a state of pain, not by invoking any concept of pathophysiology of pain or tenderness, but by finding only the requisite number of tender points.

So . . . How are patients with widespread pain, but with fewer than 11 tender points to be diagnosed? What is the correct diagnosis for those having a high tender point count but without widespread pain?

The antecedents of fibromyalgia were muscular rheumatism, fibrositis, and neuasthenia — themselves essentialist models of disease based on speculative ideas of causation. "Fibromyalgia can be seen as a fusion of the still unexplained symptoms of neurasthenia with the localized tenderness of muscular rheumatism and fibrositis."

Because a diagnosis of fibromyalgia depends solely upon clinical features in the absence of any linkage of pathology or pathogenesis, it is not surprising that heterogeneous groups of patients who present with widespread pain and tenderness have been awarded this diagnosis. (Tender at 12 or more of 18 specified anatomical sites, mostly unknown to the patient.)

"Fibromyalgia, the neurasthenia of the late 20th century, is about to follow its 19th century namesake (neurasthenia), paying yet again the penalty of a failure to distinguish between cause and effect."

Lancet March 27, 1999; 353: 1092-93 "Viewpoint", essay by John L Quintner and Milton L Cohen, first author from Wyllie Arthritis Centre, Western Australia

Comment:

Patients with fibromyalgia may be frequent attenders without identifiable pathology ("somatizers"). Is giving a label (a name) to the symptoms of a patient with somatization harmful or helpful? I fail to see the harm.

How should we relate to them?

Understand and accept the patient’s suffering; do not deny the reality of the symptoms; legitimize the patient’s suffering

Be patient; recognize uncertainty; limit referrals and iatrogenic harm; reassure.

Help the patient cope and understand the illness and improve functioning; empower patients to manage the illness themselves; direct attention to care rather than cure

Avoid labeling as "psychogenic", or "all in your head", 2) avoid simply agreeing with the patient’s own conception of the cause, 3) explain the causation in reasonable and non-threatening way. Eg, "You may have a lower threshold of pain perception — a heightened sensitivity of your central nervous system to pain. You may be more sensitive to afferent stimuli than most people." This may lead to better acceptance of the symptoms. RTJ
Recommended Reading

3-17 EVIDENCE AND ETHICS

Evidence-based medicine is advanced to answer 2 types of questions: What is best for this patient? How should we distribute health-care resources? If the intervention clearly lacks high quality evidence of efficacy, it may be discarded. However, for most medical decisions, clear guidance is not available, and the limited scope and ambiguous nature of available evidence introduces ethical concerns.

How well does evidence-based medicine help the general practitioner decide what is best for a patient?
"For general practice, evidence-based medicine provides far less guidance than it can for specialty practice."

Each day the general practitioner is confronted with various decisions of moderate, but cumulative effects on the health of a patient. Buried within are few decisions that have profound long-term effects. The tools most helpful to the general practitioner include knowledge of both the patient and the natural history of the illness, the ability to identify illness patterns, particularly early in the course of the disease, and to recognize the potential for serious illness to develop.

The main determinants of the "best" course are the physician’s judgement guided by clinical experience in the face of limited scientific evidence, and the patient’s preference. This frequently means there is not one best course of action. In the face of uncertainty, the limited input available from evidence-based medicine can be helpful, but is not a sufficient basis for decision-making.

Decisions, particularly for chronic illness, require a complex calculus that integrates the effect of potential disease states, treatment side effects, and the patient’s psychological and social responses over the long-term.

"Indeed, for many decisions, there is simply no evidence available."

"Even when available, evidence is commonly inadequate or misleading."

How well does evidence-based medicine help the specialist?

Specialty practice is better suited to an evidence-based approach. Choice is usually between fairly narrow diagnostic and treatment alternative. A few well-defined options are usually available. The use of time as a diagnostic or therapeutic strategy is rarely an option. The illness has usually progressed further. The body of evidence directly applicable to the specialist’s questions tends to be more adequate than in general practice. The base of evidence applicable is far more than that available to the general practitioner. Emphasis should be on applying evidence-based medicine to specialty care.

How are we to distribute health-care resources?

Given that the comparative value of human experience is subjective, and varies with age, sex, and culture, it is unlikely that universal metrics of the value of health-care will ever be developed. "Evidence-based medicine (especially with physiological or disease-oriented outcomes) must never take precedence over sound ethical decision making by the physician. It is wrong to assume that if an activity cannot be quantified, or has no evidence base, it is of no value."

Evidence-based medicine may distort the doctor-patient relationship. Historically, the physician has been the patient’s advocate. The priority has been to act in the patient’s best interest. The patient’s own values and decisions must be taken into account. Within this framework, evidence-based medicine is useful so long as it remains only a tool that helps inform decision-making.

The whole process of becoming a physician requires acceptance of a science-oriented value system. Evidence-based medicine can be a seductive, subtle, and distorting influence leading the physician away from the best interests of the patient and away from decisions based on the patient’s values.
An intrinsic feature of the randomization process is a disregard for the individuality of each patient, his or her specific context, and unique considerations that might influence clinical decisions.

"Primary care research, with its emphasis on outcomes, natural history, human behavior, cultural issues, and questions related to care rather than cure, is of vital importance to an understanding of our patients, their problems, and the way we can best serve them. These issues are suited to qualitative research designs, descriptive work, and case-control or cohort designs. RCT designs rarely apply."

What is the best role for evidence-based medicine?

Evidence-based medicine provides a focused approach. It focuses on average effects, and rarely provides guidance to care of the individual. It rarely provides guidance about how to respond to an individual patient’s values, priorities, and cultural needs.

Evidence-based medicine is a tool, not a standard by which resource allocations and health-services are made.

"Evidence-based medicine and the clinical pathways derived from it can aid, but should never supercede or replace, the judgement of a clinician who knows both the patient and the evidence."

Lancet March 6, 1999; 353: 829-31 "Evidence and Primary Care", commentary by Larry Culpepper, and Thomas T Gilbert, Boston University Medical Center, Mass.

1. "Efficacy" describes the value of an intervention determined by clinical trial. "Can it work?"

"Effectiveness" describes the value of the intervention when applied to the real world clinical practice. "Does it work for my patient?" (May differ greatly from efficacy.)

"Efficiency" describes the costs when the intervention is applied. "Is it worth it?"

Recommended Reading

3-18 EVIDENCE-BASED INTERVENTIONS AND COMPREHENSIVE TREATMENT

"Discussions on evidence-based medicine tend to concentrate on research methodology and reduce clinical practice to the technical implementation of research findings."

This article examines the issue of the evidence base for complex, composite intervention procedures in general practice. It reviews the target of evidence (the intervention) in relation to the target of the intervention (the patient).

"A key value of general practice is to seek maximum intervention results with minimum medical interference."

"The complexity of clinical practice can be clarified by distinguishing the disease dimension from the personal dimension. In general practice, the personal dimension predominates. In general practice the personal dimension offers a particularly rich potential for intervention."

"With the randomized, controlled trial methodology of evidence-based medicine, the convention is to ignore the consequences of the personal dimension, and instead to focus on the assessment of evidence exclusively in terms of the disease intervention."

"Evidence-based general practice can be achieved only when its personal generic efficacy is assessed in the context of its conceptual framework of care."

Lancet March 13, 1999; 353: 916-18 "Evidence and Primary Care" commentary by Chris van Weel and J Andre Knottnerus, University of Nijmegen and University of Maastricht, Netherlands
The association between dietary fat and coronary heart disease (CHD) is established. The role of dietary carbohydrate is less well recognized.

Diets with high glycemic index have been reported to increase risk of CHD and type 2 diabetes. (High glycemic-index (HGI) carbohydrates are characterized by rapid absorption and high post-prandial glucose and high insulin responses. They may lead to decreased insulin sensitivity.)

High glycemic index diets have been shown to decrease insulin sensitivity (increase insulin resistance) and lower HDL-cholesterol concentrations. This may be a potential explanation for the detrimental effects.

This study examined whether the glycemic index of dietary carbohydrate is a determinant of HDL concentrations.

Conclusion: HGI carbohydrate diet was significantly related to low HDL-cholesterol concentrations. Low glycemic carbohydrates to a higher HDL-cholesterol.

STUDY

1. Reanalysed data from the 1986-87 Survey of British Adults (n = 1420 with complete data). Examined the relationship between serum total-cholesterol, HDL-cholesterol, and the glycemic index of the diet.
2. Data calculated from detailed food-diaries included various dietary characteristics — type of carbohydrate, the glycemic index, and fat intake.
3. Calculated the glycemic index individually from previously published tables. The average glycemic index of each individual food was multiplied by the percentage contribution of each carbohydrate containing food eaten over 1 week. The sum was taken as the glycemic index for the individual.

RESULTS

1. There was a significant inverse relationship between HDL-cholesterol concentrations and the glycemic index of the diet.
2. The glycemic index was not related to total-cholesterol and LDL-cholesterol.
3. Dietary fat was not related to HDL-cholesterol concentrations.

DISCUSSION

1. The higher the glycemic index, the lower the HDL-cholesterol.
2. Total-cholesterol and LDL-cholesterol were not influenced by the glycemic index.
3. In this study, only body mass index, smoking, and glycemic index were identified as potentially modifiable risk-factors for HDL concentrations.
4. Prospective epidemiological studies support the hypothesis that high carbohydrate diets that are high in fiber and complex carbohydrates are protective against CHD and type 2 diabetes. Some studies specifically attribute this benefit to carbohydrate foods with a low glycemic index: pasta, oats, whole grain products, pulse (edible-seed bearing) vegetables such as beans and peas, and whole fruits.
5. Prospective studies have consistently shown that diets with low glycemic indices lower serum triglyceride concentrations.
6. Low glycemic index diets cause attenuated and prolonged postprandial insulin release, with lower absolute insulin concentrations. This pattern of release is more effective for suppressing lipolysis and visceral release of non-esterified fatty acids.
7. High glycemic index carbohydrates produce greater fluctuations in plasma glucose and insulin. They also stimulate production of several counter-regulatory hormones such as epinephrine and norepinephrine which may lower insulin sensitivity.

CONCLUSION

High glycemic index carbohydrate diets (increasing postprandial blood glucose concentrations) were associated with lower HDL-cholesterol concentrations; low glycemic index diets (lower postprandial blood glucose) with higher HDL-cholesterol concentrations.

The glycemic index was a stronger predictor of HDL-cholesterol concentrations than was dietary fat intake.


============================================================================

3-20 ARE THERE GOOD AND BAD CARBOHYDRATES FOR HDL CHOLESTEROL?
(This editorial comments and expands on the preceding study)

Are beans better than potatoes for blood lipids? Will substituting low glycemic-index carbohydrates for high glycemic-index carbohydrates benefit patients by raising HDL cholesterol (HDL-c)?

There is enough evidence to cause concern about anything that lowers HDL-c.

Diets low in fat necessarily have a high carbohydrate content. Low fat, high carbohydrate diets lower HDL-c (an adverse outcome) as well as LDL-c (a beneficial outcome). The HDL-c/ LDL-c ratio may remain unchanged. The recommendation to decrease fat and increase carbohydrate has come under scrutiny.

The study suggests that not all carbohydrates lower HDL-c.

The glycemic index is the area under the blood glucose curve produced by a food expressed as a percentage of the area produced by the same amount of carbohydrate eaten as white bread. The concept was introduced to help diabetic patients to minimize the blood glucose for a certain carbohydrate intake.

Surprisingly, the glycemic index is not usually low for foods rich in fiber and complex carbohydrates, and is not high for all refined foods. Wholemeal bread has the same glycemic index as white bread. White sugar has a lower glycemic index than bread. (Ordinary sugar contains 50% fructose, which has little effect on postprandial glucose.)

Foods with a consistently low glycemic index include beans, peas, spaghetti, and some fruits.

The dietary glycemic index was positively associated with the risk of coronary heart disease in the Nurses’ Health Study.

"The results of this study should be interpreted with caution."


Comment:

The editorialist lists the glycemic index of some foods as a % of the glycemic index of white bread:

<table>
<thead>
<tr>
<th>Food</th>
<th>Glycemic Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>138</td>
</tr>
<tr>
<td>Instant rice</td>
<td>128</td>
</tr>
<tr>
<td>Baked potato</td>
<td>121</td>
</tr>
<tr>
<td>Corn flakes</td>
<td>119</td>
</tr>
<tr>
<td>Food</td>
<td>Value</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------</td>
</tr>
<tr>
<td>White bread</td>
<td>100</td>
</tr>
<tr>
<td>Sucrose</td>
<td>92</td>
</tr>
<tr>
<td>Apples</td>
<td>52</td>
</tr>
<tr>
<td>Kidney beans</td>
<td>42</td>
</tr>
<tr>
<td>Milk</td>
<td>39</td>
</tr>
<tr>
<td>Red beans</td>
<td>36</td>
</tr>
</tbody>
</table>

The idea is to lower the postprandial area under the glucose curve, thus lowering insulin response. This concept fits with some of the healthy diet concept — fruits, vegetables.

Would not eating smaller amounts frequently (as opposed to gouging) accomplish the same? RTJ

3-21 THE PHYSICAL CONSEQUENCES OF DEPRESSIVE ILLNESS

There is important and accumulating evidence that the physical consequences of depression are far from benign. In particular, increased risk of coronary artery disease and osteoporosis have received attention.

One 55-year prospective study examined the relation between mood disorder and physical health. After controlling for confounding factors, among 237 healthy men recruited at college entry and assessed at age 70, 45% of those who had suffered a depressive episode were dead at follow-up compared with 5% of those in good psychological health.

Another study found that major depression increased the risk of coronary disease, with a mean lag of 10 years. Another study of over 2400 men reported, among those without prior history of cardiac disease, those who suffered a depressive episode were at a significantly greater risk of myocardial infarction. Another reported a cohort of 1500 men — risk of myocardial infarction rose 4-fold after a major depression.

Similarly clear-cut findings have been reported in relation to bone mineral density (BMD). Women with current or past depression had decreased BMD, lower osteocalcin levels (an indicator of bone formation) and higher urinary free cortisol excretion. (Hypercortisolism decreases BMD and redistributes body fat to the abdomen, and increases risk of coronary artery disease.)

The most consistent biologic abnormality in major depression is increased activation of the hypothalamic-pituitary-adrenal axis.

Depression is an illness with physical as well as social and psychological consequences.

BMJ March 27, 1999; 318: 826 Editorial by Timothy G Dinan, Royal College of Surgeons in Ireland, Dublin

REFERENCE ARTICLE

3-22 POSTEXPOSURE CHEMOPROPHYLAXIS FOR OCCUPATIONAL EXPOSURES TO THE HUMAN IMMUNODEFICIENCY VIRUS

This article considers: safety and efficacy of antiretroviral chemoprophylaxis and suggested clinical management. A table (p 934) presents the US Public Health Service recommendations for postexposure regimens.
The efficacy of postexposure chemotherapy is by no means iron-clad. Several instances of failure following occupational exposure have been carefully documented. But, "offering postexposure chemotherapy for occupational exposures to HIV remains an entirely rational approach to this complex problem."

JAMA March 10, 1999; 281: 931-36 "Grand Rounds" seminar by David K Henderson, National Institutes of Health, Bethesda, MD