

# PRACTICAL POINTERS

FOR

## PRIMARY CARE

ABSTRACTED MONTHLY FROM THE JOURNALS

**NOVEMBER 2001**

REPAGLINIDE (*PRANDIN*) A NEW ORAL DRUG FOR DIABETES

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FONDAPARINUX, A NEW ANTICOAGULANT

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS AND THE RISK OF ALZHEIMER'S DISEASE

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# HIGHLIGHTS NOVEMBER 2001

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## **11-1 INSULINOTROPIC MEGLITINIDE ANALOGUES: Repaglinide (*Prandin*); A New Oral Drug**

New oral insulinotropic drugs are coming on the market. They act quickly to release insulin into the portal circulation and liver when given shortly before meals. They reduce hyperglycemia by an immediate action on the liver which impairs glucose output. They are less likely to produce hypoglycemia. Dosing schedules may be more flexible.

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## **11-2 CLINICAL INERTIA**

Medicine has traditionally focused on relieving patient symptoms. However, maintaining good health increasingly involves management of such problems as hypertension, dyslipidemia, and diabetes, which often have no symptoms. Abnormal BP, lipid, and glucose values are generally sufficient to warrant treatment without further diagnostic maneuvers. These commentators focus on limitations in managing such problems in everyday practice. They term this "clinical inertia"-- recognition of the problem but failure to act -- failure of clinicians to initiate or intensify therapy when indicated.

## **11-3 WHY GENERAL PRACTITIONERS DO NOT IMPLEMENT EVIDENCE**

"General practitioners seem to regard clinical evidence as a square peg to fit a round hole in the patient's life." The process of implementation of evidence-based medicine is complex, fluid, and adaptive.

Decisions are influenced by the doctor's personal and professional experience as well as by their knowledge of and relationship with the patient.

## **11-4 IMPACT OF HIGH-NORMAL BLOOD PRESSURE ON THE RISK OF CARDIO-VASCULAR DISEASE.**

High normal BP (130-139/85-89) was associated with an increased risk of cardiovascular disease.

Practical point: Would not lowering "high normal" BP (130-139/85-89) in individuals at high risk due to a combination of factors seem reasonable? Certainly, life style measures are indicated. Drug therapy should be reserved for those with multiple risk factors, addressing all factors at the same time.

## **11-5 ASSESSMENT OF FREQUENCY OF PROGRESSION TO HYPERTENSION IN NON-HYPERTENSIVE PARTICIPANTS IN THE FRAMINGHAM HEART STUDY**

Normal (120-129/80-85) and high normal (130-139/85-89) frequently progressed to hypertension >140/90) over 4 years, especially in older overweight adults. This supports the recommendation for monitoring those with high normal BP every year, those with normal BP every 2 years.

Control of weight and weight gain is important for primary prevention.

Practical point: regular screening for hypertension is a major responsibility of primary care clinicians. Weight control is also a major challenge. Development of systolic hypertension seems almost inevitable as age progresses. When to treat isolated systolic hypertension is another major challenge.

## **11-6 SIMVASTATIN AND NIACIN, ANTIOXIDANT VITAMINS, OR THE COMBINATION FOR THE PREVENTION OF CORONARY DISEASE.**

Compared with placebo, combined niacin-statin (simvastatin) provided marked clinical and angiographic benefits in patients with established coronary disease and low HDL levels. (Secondary prevention). The decrease in LDL related to combined statin-niacin was greater than the average decrease reported from statin therapy alone. The increase in HDL was much more than usually reported from statins alone. The rate of major clinical events was reduced by 90% in the simvastatin + niacin group.

Antioxidants did not benefit. "Unless more compelling evidence appears, we see little justification for the use of antioxidant vitamins for the prevention of cardiovascular events."

### **11-7 THE SAFETY OF INACTIVATED INFLUENZA VACCINE IN ADULTS AND CHILDREN WITH ASTHMA.**

"Influenza vaccine does not worsen asthma." Current guidelines for the immunization of patients with asthma are safe. In a large diverse group of adults and children with asthma, adverse effects were no more common in those receiving flu vaccine than in those receiving placebo injections.

Practical point: Health care providers should urge patients with asthma to be immunized and thus reduce the morbidity associated with influenza. Patients may be reassured by referring them to this study.

### **11-8 PYRAZOLOPYRIMIDINES**

Zaleplon (*Sonata*) has many attributes of the ideal hypnotic agent — rapid absorption, rapid onset, adequate duration of action, minimum or no residual effect on daytime performance, and no evidence of pharmacological tolerance or withdrawal. "It provides another very helpful option in the management of patients with insomnia."

### **11-9 ANTIOXIDANTS AND ZINC TO PREVENT PROGRESSION OF AGE-RELATED MACULAR DEGENERATION**

Persons older than 55 years should have dilated eye examinations to determine the risk of developing advanced ARMD.

Practical point: Those with extensive intermediate size drusen, at least one large druse, non-central geographic atrophy in one or both eyes, or advanced ARMD or vision loss, and without contraindications such as smoking (which may increase adverse effects of beta carotene) should consider taking a supplement of antioxidants plus zinc such as used in this study.

### **11-10 LEGUME CONSUMPTION AND RISK OF CORONARY HEART DISEASE IN US MEN AND WOMEN**

A significant benefit in reducing incidence of cardiovascular disease was associated with increased legume consumption of at least 4 servings weekly.

### **11-11 DECREASED RATE OF CORONARY RESTENOSIS AFTER LOWERING OF PLASMA HOMOCYSTEINE LEVELS.**

Treatment with a combination of folic acid (400ug), vitamin B12 (400 ug) and B6 (pyridoxine 10 mg) was associated with a significant reduction in the rate of restenosis after PTCA.

### **11-12 A COMPARISON OF WARFARIN AND ASPIRIN FOR THE PREVENTION OF RECURRENT ISCHEMIC STROKE.**

Over a 2 year period, there was no difference between aspirin and warfarin in prevention of recurrent non-cardiac stroke or death. For more than 50 years, physicians have prescribed warfarin for patients with non-cardioembolic stroke in the hope that subsequent strokes could be prevented. This treatment was based on a mixture of clinical experience, observational studies, and inferences about the pathophysiology of stroke.

"Aspirin alone, or in combination with some other antiplatelet agents appears to be a well-justified choice for the prevention of recurrent ischemic stroke"

Practical point: This simplifies secondary prevention.

### **11-13 THE PATIENT WITH HYPOCHONDRIASIS**

Although there is no definitive therapy, physicians can effectively care for patients with hypochondriasis by acknowledging that somatic symptoms without a medical basis can be as distressing as those resulting from demonstrable disease. The goal of treatment should be to improve coping with symptoms rather than their elimination, as in the management of chronic physical illness. This approach minimizes the frustration of both the patient and the physician.

Patients with hypochondriasis are a subgroup of patients who somatize — namely those whose medically unexplained symptoms are accompanied by an unshakable conviction that they have a serious disease. Overlap exists.

There is good evidence that vigorous treatment of psychiatric disorders that frequently

co-exist are responsive to drugs. Drug treatment may help resolve hypochondriacal symptoms associated with major depression, panic disorder, and obsessive-compulsive disorder.

#### **11-14 HORMONE REPLACEMENT THERAPY AND DRY EYE SYNDROME**

Postmenopausal women who used HRT had a higher prevalence of dry eye syndrome compared with never-users. Those using estrogen alone are more affected.

#### **11-15 A SIMPLE RISK INDEX FOR RAPID INITIAL TRIAGE OF PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION**

A simple risk index based on age, heart rate, and systolic BP captured most of the information from more complex tools. Risk rose sharply after age 60, after a pulse rate of 80, and when systolic BP fell below 120. The index is likely to be useful in rapid triage of patients with ST-elevation acute MI.

Practical point: This assessment could be a useful indicator for immediate use of a new bolus fibrinolytic agent at the primary encounter site.

#### **11-16 CHOOSING A PARENTERAL ANTICOAGULANT AGENT**

Fondaparinux is derived from the activated factor X (Xa) binding moiety of unfractionated heparin.

Two studies<sup>1,2</sup> report that once-daily treatment initiated early in the postoperative period was more effective than LMWH in preventing venous thromboembolism after hip and knee surgery.

Fondaparinux has been approved by the FDA for prevention of thromboembolism after orthopedic surgery. (*Arixtra*)

#### **11-17 NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND THE RISK OF ALZHEIMER'S DISEASE**

Long-term use of NSAIDs may have a beneficial effect in preventing AD. "Primary-prevention trials should be undertaken to confirm this finding and show whether the benefits of such therapy outweigh the risks."

Practical point; None at this time. We need more information on the benefit/harm-cost. Primary care clinicians should be aware of this putative linkage. Patients may be asking about it.

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### ***A review of pathophysiology of type 2 diabetes and a new oral drug***

#### **11-1 INSULINOTROPIC MEGLITINIDE ANALOGUES:**

##### **Repaglinide (*Prandin*); A New Oral Drug**

###### *Pathophysiology of type 2 diabetes:*

Insulin resistance precedes type 2 diabetes by many years. During this period, insulin production and secretion from the pancreas increase to counter the insulin resistance. Overt hyperglycemia occurs when insulin secretion can no longer overcome the level of insulin resistance. For an individual to remain glucose tolerant, insulin responses must be sufficient to match any increase in insulin resistance. Thus, good beta-cell function can protect against diabetes even in the face of increasing insulin resistance. "It is compromised beta-cell function that is a prerequisite for type 2 diabetes."

Obesity is an important contributor to insulin resistance. Daily insulin secretion is three-fold higher in glucose tolerant obese patients than in non-obese controls. Obese persons develop type 2 diabetes when they are unable to sustain the required level of hyperinsulinemia.

When the available insulin is inadequate the liver increases output of glucose, and glucose uptake by peripheral tissues is impaired. Hyperglycemia results.

*Importance of  $\beta$ -cell function:*

A. *Post oral glucose insulin production:* Glucose initiates an early insulin response made up of 2 phases:

- 1) *The first phase* insulin response peaks at 3 to 5 minutes and is over by 10 minutes. This represents the release of a small pool of preformed and readily accessible secretory vesicles. Persons at risk of type 2 diabetes lose this phase of insulin response. Abnormal immediate-phase secretion has been described in normoglycemic women who have a history of gestational diabetes. First degree relatives of patients with type 2 diabetes are at lower risk of developing diabetes if their immediate-phase insulin response is normal. And are at high risk of developing diabetes if their immediate-phase insulin response is impaired.
- 2) *A second-phase* response to glucose ingestion occurs in which insulin concentrations rise steadily to a much lower peak. From about 2 minutes after glucose ingestion, plasma insulin concentrations are maintained until normoglycemia is achieved. This relies on mobilization of a stored pool of insulin and de novo insulin synthesis by the pancreas.

B. *Basal insulin production:* Under basal fasting conditions, insulin is released as discrete particles about every 10 minutes. A slower cycle is superimposed, with a periodicity of about 120 min.

*Defects in insulin pulsatility:*

Pulsatility of insulin secretion optimizes its action. Insulin given as intravenous pulses has greater activity than insulin given by continuous infusion. In impaired glucose tolerance and type 2 diabetes, alterations in pulse mass, pulse frequency, and orderliness occur. A reduction in preformed insulin-secretory vesicles contributes to reduction in the size of the insulin pulse. The small pool of preformed insulin in the pancreas is replenished overnight when demand for insulin secretion is lowered. Pulse formation is then returned toward normal. If demand for insulin remains high during the fasting state (ie continuing hyperglycemia at night), basal insulin production is stressed and formation of stored insulin in the pancreas is impaired. Nighttime hyperglycemia should be controlled.

Normally, insulin is released into the portal vein and undergoes extensive hepatic clearance before its subsequent pulsatile delivery into the peripheral circulation. This physiological delivery is associated with optimal insulin action. Ideally, a pharmaceutical agent should restore early-phase insulin secretion directly into the portal vein, and optimize suppression of hepatic glucose output and minimize postprandial hyperglycemia. (Subcutaneous insulin lacks much of this effect.)

Because insulin-mediated glucose uptake normally occurs almost exclusively in the postprandial state, the metabolic consequences type 2 diabetes are very closely linked to the postprandial glucose metabolism .

In Western society, little of the day is spent fasting. Increasing proportions of the day are in the postprandial and/or post absorptive state. It is not surprising that postprandial hyperglycemia is a greater contributor to glucose

control than is the fasting plasma glucose. Therapies that target postprandial glucose are more effective in lowering HbA1c concentrations than those aimed at lowering fasting glucose.

Unfortunately, the correction of postprandial hyperglycemia in type 2 diabetes has proved elusive.

*Pharmacological approaches to type 2 diabetes:*

Fast-acting insulin analogues help to mimic the immediate rise in plasma insulin. These agents improve glucose tolerance. Although subcutaneous insulin does suppress hepatic production of glucose, its main site of function is peripheral.

Ideally, a pharmacological agent should restore early insulin release into the portal circulation and optimize suppression of hepatic glucose output and minimize postprandial hyperglycemia.

Oral agents that specifically target the defects in beta-cell function are emerging. They are aimed at restoring the physiological early post prandial delivery of insulin. These are derived from a non-sulfonylurea moiety now termed meglitinide.

In tackling postprandial hyperglycemia, the importance of the form of *dietary* carbohydrate and its rate of absorption should not be forgotten. The blood glucose response to meals is consistently reduced when the dietary carbohydrates are in the form of soluble non-polysaccharides that are slowly absorbed (ie, have a low glycemic index; eg, pastas, whole grain bread, and lentils).

Repa-glinide (*Prandin*)

The article discusses three "glinide" drugs. (*I abstract only the data on repa-glinide since it is available in the US by prescription [Prandin] RTJ*) Its pharmacodynamic and pharmacokinetic properties provide it with a potential advance in treatment.

Repaglinide taken before a meal induces a rapid postprandial insulin response. It has a short half-life. Insulin concentrations peak at 1 to 2 hours. By 6 hours insulin is back at fasting concentration. Repaglinide is not detectable in the circulation after 4 hours, so there is little risk of hypoglycemia if the patient misses the next meal. The risk of severe hypoglycemia is less than half that seen with traditional sulfonylureas.

In one study, repaglinide, taken before each meal, was shown to be more effective than the short acting sulfonylurea glipizide (*Glucotrol*; generic). HbA1c and fasting blood glucose were reduced more effectively. Eating habits became less restricted. While taking glipizide, patients reported eating even when they were not hungry for fear of hypoglycemia. Flexible mealtime dosing of repaglinide provides an opportunity for overweight patients to diet and to lose weight. The need for snacks between meals is removed.

Repaglinide can be used in combination with other agents. It is effective when combined with metformin (*Glucophage*).

Will agents that produce immediate insulin release preserve beta-cell function and delay and prevent functional beta-cell loss? The answer will be known only after long-term trials.

Comment:

Give your pancreas a break. Don't over work it. Allow it to rest and reform and store insulin.

Therapies that target postprandial glucose are more effective in lowering HbA1c concentrations than those aimed at lowering fasting glucose. Studies have confirmed a better correlation between risk of cardiovascular disease for postprandial glucose concentrations than for HbA1c of fasting glucose.

This report stresses the importance of delivery of insulin directly into the portal vein and liver. The immediate post prandial insulin pulse acts on the liver to reduce glucose output and improve postprandial glucose concentrations. Repa-glinide may be a step in this direction. Although certainly not a perfect answer, it has advantages over subcutaneous insulin and sulfonylureas. It provides a more rapid effect on suppressing hepatic glucose output, and a shorter duration of action. If sulfonylureas are used, would it not be reasonable to prescribe them three times a day before meals to take advantage of an immediate boost in insulin delivery to the liver?

Prandin costs about \$0.85 a tablet wholesale -- three daily tablets in excess of \$3. This is considerably more than glipizide (generic for *Glucotrol*).

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## **Recognition of the problem, but failure to act in managing of silent problems**

### **11-2 CLINICAL INERTIA**

Medicine has traditionally focused on relieving patient symptoms. However, maintaining good health increasingly involves management of such problems as hypertension, dyslipidemia, and diabetes, which often have no symptoms. Abnormal BP, lipid, and glucose values are generally sufficient to warrant treatment without further diagnostic maneuvers. These commentators focus on limitations in managing such problems in everyday practice. They term this "clinical inertia"-- recognition of the problem but failure to act -- failure of clinicians to initiate or intensify therapy when indicated.

What causes clinical inertia? Clinical inertia is a problem of the health care profession and the health care system. It is a problem aside from related issues such as patient non-adherence to advice and medications, failure to return for office visits, costs, and adverse effects. It is failure of clinicians to initiate and advance best evidence medicine and guidelines.

Clinical inertia is due to at least 3 problems:

Overestimation of care provided.

Use of "soft" reasons to avoid intensification of therapy

Lack of physician education, training and practice organization aimed at achieving therapeutic goals.

*Overestimation of care provided:*

"Most providers are unaware of the limitations of their care. They overestimate their adherence to guidelines. For example, in patients with diabetes, clinicians overestimate the frequency of foot examinations, dilated eye examinations, HbA1c measurement, and urine protein screening.

*Use of "soft" reasons to avoid intensification of therapy:*

Potential rationalizations or barriers to care include: concerns about whether results from large

studies in a research environment can legitimately guide decision-making for individual patients in a more typical clinical setting, potential side effects or interactions with other medications, and patient aversion to medical therapy. Although what appears to be clinical inertia may actually be an appropriate response to the patient who wants "caring" rather than "management of silent problems", it would be hard to determine in such cases whether the patient has been, or should be, adequately informed about benefits and risks of preventive interventions.

*Lack of physician training and practice organization focused on therapeutic goals:*

"Physicians may not have been taught, and may not appreciate, the extent to which escalation of dosage and polypharmacy are needed for disease management. Physicians have little training and experience in "treating to target". (Ie, *treating to the "max"*). Emphasis on intensifying therapy to meet standard-of-care goals are uncommon in most medical schools and residency programs. The routine use of preventive medicine checklists and diabetes flow sheets has been shown to improve care, but most physicians have not been taught this need.

"Excellence in patient care will always be partly limited by a lag in dissemination of knowledge. After an advance in clinical understanding, translation of this advance into revised guidelines for practice, and incorporation of the guidelines leading to upgraded physician behavior may take 5 to 10 years."

The commentators believe that clinical inertia can be overcome. But, simple guidelines delivered in the traditional conference lecture setting often have little benefit. They suggest a need to structure routine practice to facilitate effective management of disorders for which resolution of symptoms is not sufficient to guide care. Use of reminders (such as check lists) and targeted feedback on performance are often more effective in altering clinical performance. Reminders may be computerized or simply placed on flow sheets. They appear to be effective in reinforcing clinical practice, prompting the clinician to take immediate action while the patient is present. "It seems likely that the best approach to avoiding clinical inertia is to combine flow-sheets/reminders and feedback on performance." (Ie, regular interaction with peers or opinion leaders to obtain feedback.) "Physicians will need to build into their practice a system of reminders and performance feedback to ensure necessary care." This approach must be accompanied by the realization that rigid insistence of guidelines could result in overtreatment and inappropriate actions. Individualization of care is important.

Annals Int Med November 6, 2001; 135: 825-34 "Perspective", Commentary, first author Lawrence S Phillips, Emory University School of Medicine, Atlanta, Georgia. [www.annals.org](http://www.annals.org)

Comment:

I enjoyed this provocative article. The main points are: 1) check lists will help us to review treatment schedules periodically and 2) we should increase treatments when target goals are not reached. I agree with their comments on check lists. I disagree on treatment to the "max".

Check lists would be a helpful reminder to primary-care medicine. They can be short, simple, and consulted at every office visit, although not necessarily acted upon at every visit. Airline pilots may still use them when preparing to take off or land. For example, a check list for patients with diabetes might include:

Diet	Drugs
Physical activity	Oral hypoglycemics, insulin
Weight, BMI, and abdominal circumference	Aspirin
Eyes	Statins
Feet	ACE inhibitors
Peripheral atherosclerosis (Ankle/brachial index)	Antihypertension drugs
BP	
HbA1c	
Nephropathy (Microalbuminuria; Creatinine)	
Neuropathy (Symptoms)	
Smoking	

Check lists can overcome the inertia of starting and continuing treatments and observation.

But, I believe primary care clinicians will often oppose treatment to the "max" for several reasons:

A. Difficulties in defining and reaching the best lower limits of BP, lipids, and glucose. All 3 factors present a sliding scale of risk. There is no defined cut point between where risk exists and no-risk occurs. Benefit/no-benefit is not defined at a fixed level. Attempting to attain the recommended lower limit (eg, LDL-cholesterol < 100; systolic BP < 120; HbA1c < 6%) may require increasing the dose of a single drug or adding multiple drugs. Pushing the limit will add adverse effects and costs, and limit patient-adherence. Clinical exuberance is the opposite of clinical inertia. Both may lead to inappropriate therapy.

B. As the "best" levels of risk markers are approached, diminishing returns and increase in adverse effects set in. For example, if the patient has reached a systolic BP of 140, the benefits from pushing antihypertension drugs to achieve a systolic BP of 120 will be much less than benefits from reducing BP from 180 to 140. Adverse events, costs, and inconvenience will be added. Primary care clinicians struggle to define the practical lower limits of BP, lipids, and glucose in each individual patient. Clinicians and patients may very well choose to let well enough alone. Even the best evidence-based care by the most experienced clinicians may not reach targets. (Note the lack of reaching a goal for body mass index in diabetes and the failure to achieve a HbA1c < 6%).

*(See the following abstract.)*

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### 11-3 WHY GENERAL PRACTITIONERS DO NOT IMPLEMENT EVIDENCE

Although evidence based medicine (**EBM**) has heightened awareness of the most effective management strategies for many conditions, much of the evidence is not acted on in everyday clinical practice. There may be unique barriers to implementing evidence in general practice within a patient-centered context. This study explored the reasons general practitioners do not always implement best evidence.

## STUDY

1. Qualitative study of 19 general practitioners in 3 focus groups asked participants to discuss their behavior in individual cases.
2. Each meeting focused around case notes of a particular patient, the doctor-patient relationship, and the feelings that were generated.
3. Group members were asked to present details of a case in which he or she had knowingly not followed evidence-based practice. The group discussed the case and explored implementation issues arising from it, as well as the doctor's feelings about these issues.
4. The main clinical areas discussed included hypertension, ischemic heart disease, and anticoagulation.

## RESULTS

1. Six main themes emerged that indicated barriers to implementation:
  - A. *Personal and professional experience*: Enthusiasm for the evidence and the way it was implemented varied. The process of implementing clinical evidence was affected by the personal and professional experience of the doctor. Mishaps or spectacular successes had a direct influence on subsequent practice. (Eg., a severe bleeding episode resulting from warfarin use for a patient with non-rheumatic atrial fibrillation might make the clinician somewhat reluctant to prescribe it again.)
  - B. *Doctor's relationship with individual patients*: Evidence, even if extremely good, was interpreted in the context of the individual patient. (Eg, patients may resist taking certain drugs because of a history of adverse effects in family members.) The views of the patient modified how and when doctors applied the evidence.
  - C. *Perceived tension between primary and secondary care*: General practitioners approached evidence-based practice differently than specialists. GPs treat patients rather than diseases. They considered specialist care much more controlled than the "real life" of general practice. (Eg, hypertensive patients often feel well. They are just running a risk. "We give them a drug with a side-effect which changes the quality of their life.")
  - D. *Clinical evidence can evoke feelings among doctors and patients*: For the doctors in the study, clinical evidence was not just an intellectual commodity that is lifted from medical journals and transferred to a patient. Applying EBM, as well as failing to act on EMB, may cause anxiety in both doctor and patient. Nevertheless, they recognized that EBM can change practice within a week.
  - E. *Words by doctors can influence patients' decisions*: Doctor's choice of words can sway patients to either accept or reject clinical evidence. Doctors realize this and can use it to pre-empt patients' decisions. The way doctors present the evidence to patients may effectively limit the options patients may choose while seeming to invite the patient to make the decision. The semantics used affect the way in which evidence is implemented by swaying the patient in a particular direction. There is a tension between encouraging autonomy and effectively limiting options by a slanted presentation.

F. *Logistics of general practice*: EBM comes up against logistical problems which affect how EBM is applied. Starting a new treatment may be considered a "hassle", "risky", or "hard work" for both doctors and patients. Changing medications may create anxiety and entail frequent visits to try to reassure the patient. Knowing the patient's personal situation influences implementation.

2. Implementation of EBM by primary care clinicians is a complex and fluid process.
3. Scientific research and general practice have been described as being parallel universes. The doctors in this study were exploring personal importance — that is, the "key to transfer of an idea to, and the evaluation and interpretation of an idea by, the doctor and patient together". Evidence is not implemented in a simple linear way as some definitions of EBM imply. It is an evolving process whereby reciprocal contributions by the doctor and the patient over time influence how evidence ultimately is used.
4. Although there was plenty of evidence that the doctors were implementing evidence and were happy to do so, sometimes sticking strictly to the rules of guidelines is not appropriate.

## CONCLUSION

"General practitioners seem to regard clinical evidence as a square peg to fit a round hole in the patient's life." The process of implementation of evidence-based medicine is complex, fluid, and adaptive.

Decisions are influenced by the doctor's personal and professional experience as well as by their knowledge of and relationship with the patient.

BMJ November 10, 2001; 323: 1100-02 "Primary Care" first author A C Freeman, School of Postgraduate Medicine and Health Sciences, Exeter, UK [www.bmj.com/cgi/content/full/322/7321/1100](http://www.bmj.com/cgi/content/full/322/7321/1100)

Comment:

There is another important problem: there may be no valid evidence to fit an individual patient. Many randomized controlled trials begin by recruiting a cohort of patients, then exclude many for various reasons. A trial may begin with 1) 2000 possible subjects and then 2) exclude 500 for not meeting the entrance criteria, another 250 may withdraw for personal reasons, another 250 may develop adverse effects and withdraw. This leaves 1000 for whom evidence is not applicable in primary care.

The primary care clinician's question then is— What do you do if the next patient you see fits into category 2)?

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*Is "high-normal", normal?*

## **11-4 IMPACT OF HIGH-NORMAL BLOOD PRESSURE ON THE RISK OF CARDIO-VASCULAR DISEASE.**

Epidemiological studies have demonstrated that systolic and diastolic BPs have a "strong, continuous, graded, and etiologically significant" positive association with cardiovascular disease outcomes.

This study asks —is "high-normal" BP (130-139/85-89) associated with increased risk?

Conclusion: High-normal BP is associated with increased risk compared with normal BP and optimal BP.

## STUDY

1. The Framingham Heart Study followed over 6800 patients (mean age = 48) . All were free of hypertension (all below 140/90), and cardiovascular disease at baseline.
2. At baseline determined the association between BP category (optimal; normal; and high-normal — the Joint National Committee classification) and incidence of cardiovascular disease on follow up of 10 years.
3. Subjects in the high-normal group were not treated with antihypertension medication.

## RESULTS

1. Baseline characteristics:

	Optimal BP (< 120/80) (N = 2900)	Normal (120-129/80-84) (N = 2200)	High normal (130-139/85-89) (N = 1800)
Mean BP			
Women	108/70	122/72	132/81
Men	111/71	122/78	131/83

2. Age-adjusted cumulative incidence (10 year) of first cardiovascular event (%):

	Optimal	Normal	High normal
Women	1.9	2.9	6.4
Men	5.8	7.6	10.3

3. The 10-year cumulative incidence of cardiovascular disease in subjects with high normal BP:

Ages 35-64 Women = 4%	Men = 8%
Ages 65-90 Women = 18%	Men = 25%

4. Compared with those with optimal BP, a high-normal BP was associated with a risk ratio for cardiovascular disease of 2.5 for women and 1.6 for men.

## DISCUSSION

1. Persons with high-normal BP (130-139/85-89) at baseline had a higher incidence of cardiovascular disease over 10 years follow-up than those with optimal BP (<120/80). A continuous gradient across the 3 non-hypertensive BP categories (optimal; normal; high normal) was observed.
2. Risks persisted after adjustment for other cardiovascular risk factors.
3. The rate of cardiovascular events was low among persons with optimal BP.
4. Whether lowering BP from high-normal to normal or optimal will improve prognosis is not known.
5. We need additional research to determine if persons with high-normal BP who are at high risk (eg, elderly, diabetes, multiple risk factors) will benefit from lowering high-normal BP.

## CONCLUSION

High normal BP (130-139/85-89) was associated with an increased risk of cardiovascular disease.

NEJM November 1, 2001; 345: 1291-97 Original investigation, first author Ramachandran S Vasam, Framingham Heart Study, and Boston University School of Medicine, Boston, Mass. [www.nejm.org](http://www.nejm.org)

Comment:

This is another example of the risks of cardiovascular events which begin with those in the lowest category of risk factors (eg, lipids, blood glucose, insulin resistance, albuminuria, as well as BP) and rise in a graded manner. There is no distinct cut-point between risk and no-risk.

When should treatment begin? Certainly all patients with high-normal BP should be treated with life-style measures, directed not only at BP, but at all risk factors. Drug therapy is another matter. As the study states, we do not know if lowering high normal BP to optimal BP will reduce risk. It would be reasonable to assume so.

Weighing costs and adverse effects, I would consider low-dose drug therapy for those with multiple risk factors, while targeting all risk factors simultaneously. RTJ

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### **11-5 ASSESSMENT OF FREQUENCY OF PROGRESSION TO HYPERTENSION IN NON-HYPERTENSIVE PARTICIPANTS IN THE FRAMINGHAM HEART STUDY**

Blood pressure and the prevalence of hypertension increase with age. Periodic screening is advised.

Knowledge of the rates and determinants of progression from normotension to hypertension is critical for defining the optimum BP screening interval for individuals without hypertension. Guidelines for screening vary widely.

This study assessed the rates of progression to hypertension and the determinants of progression to hypertension among the Framingham cohort. This was an attempt to establish the best frequency of screening.

Conclusion: Individuals with optimum BP as well as those with "high normal" BP frequently progressed to hypertension over 4 years.

#### **STUDY**

1. Periodically measured BP in over 9500 individuals without hypertension (< 140/90).

Mean age = 52; primarily Caucasian.

2. Defined optimum BP as > 120/80; normal as 120-129/80-85, and high normal as 130-139/85-89

3. Determined development of hypertension ( $\geq 160/100$ , and use of antihypertension medication) over 4 years.

#### **RESULTS**

1. A stepwise increase in incidence of hypertension occurred across 3 non-hypertensive categories:

A. Participants below age 65

BP at baseline	Developed hypertension
Optimum	5%
Normal	18%

High normal 37%

B. Participants over age 65 progressed more frequently: 16%; 26%; and 50%.

2. Obesity and weight gain contributed to progression. A 5% weight gain over 4 years was associated with a 20-30% increased odds of developing hypertension.
3. Progress to hypertension was determined on the basis of an increase in systolic alone in 45%; diastolic alone in 11%; increase in both in 12%; use of antihypertension drugs in 32%.

## DISCUSSION

1. Over 4 years, after a mean age of 52, a stepwise increase occurred in incidence of hypertension across 3 non-hypertensive BP categories (optimum, normal, and high normal).
2. Older individuals and those with high normal BP were more likely to progress. Sex was not an important determinant.
3. Baseline body-mass index (**BMI**) and weight gain were important determinants of progression
4. Development of isolated systolic hypertension was, by far, the most common.
5. A substantial proportion of those in the high normal group developed hypertension within 1 year of follow-up. This suggests a yearly screening in this group.
6. Less frequent monitoring might be appropriate in younger persons with optimum BP.

## CONCLUSION

Normal (120-129/80-85) and high normal (130-139/85-89) frequently progressed to hypertension (>140/90) over 4 years, especially in older overweight adults. This supports the recommendation for monitoring patients with high normal BP every year, those with normal BP every 2 years.

Control of weight and weight gain is important for primary prevention.

Lancet November 17, 2001; 358: 1682-86 Original investigation from the National Heart, Lung and Blood Institute's , Framingham Heart Study, first author Ramachandran W Vasan [www.thelancet.com](http://www.thelancet.com)

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### *A common sense combination*

#### **11-6 SIMVASTATIN AND NIACIN, ANTIOXIDANT VITAMINS, OR THE COMBINATION FOR THE PREVENTION OF CORONARY DISEASE.**

Epidemiologic studies predict that for each 1% reduction in LDL-cholesterol there will be about a 1% reduction in risk of major cardiovascular events. Similarly, because of the protective effect of HDL-cholesterol, a 2% to 3% increase in HDL is associated with a 2% to 4% reduction in risk.

If the benefits of increasing HDL and decreasing LDL are independent and of similar magnitude, then simultaneous therapeutic alterations of levels of these lipoproteins should theoretically produce an additive effect. (Niacin primarily raises HDL; statins primarily lower LDL.)

Antioxidant vitamins have also been reported to benefit patients with coronary disease.

This study assessed the possible benefits of combined niacin + simvastatin as well as antioxidant vitamins.

Conclusion: Simvastatin + niacin produced marked benefits. Antioxidant vitamins did not benefit.

## STUDY

1. Randomized, double-blind trial entered 160 patients. All had documented coronary disease.  
(Ie, a secondary prevention trial.)
2. All had low HDL levels ( $> 35$  mg/dL in men and  $< 40$  mg/dL in women) as well as "normal" LDL levels, defined as below 145 mg/dL).<sup>1</sup>
3. Randomized to one of four regimens:
  - A. Simvastatin (*Zocor*) + niacin (slow release [*Slo-Niacin*] or crystalline [*Niacor*]).  
(See text p. 1584 for protocol ) Mean dose of simvastatin = 13 mg/d. Mean dose of niacin = 2.4 g/d.
  - B. Antioxidants (Vitamin C, vitamin E, carotene, and selenium).
  - C. Simvastatin + niacin + antioxidants.
  - D. Placebos.
4. End-points = change in coronary stenosis by angiography, and the occurrence of a first coronary event (death, non-fatal MI, cerebral infarction, revascularization, hospitalization for ischemia).
5. Follow-up = 3 years.

## RESULTS

1. In the simvastatin + niacin group, LDL was lowered by 42% and HDL was raised by 26% .
2. Antioxidants actually reduced benefits when added to simvastatin + niacin. The protective increase in HDL was blunted by addition of antioxidants. (+ 9 mg/dL vs + 6; a surprise finding. )
3. Average coronary stenosis (by angiography) *progressed* by 4% with placebos, 2% with antioxidants, 0.7% with the simvastatin + niacin + antioxidants, and *regressed* by 0.4% in the simvastatin + niacin group.
4. Frequency of clinical end-points over 3 years: placebo — 24%; antioxidants alone — 21%; simvastatin + niacin + antioxidants — 14%; simvastatin + niacin — 3%.
5. Adverse effects: Compliance ranged from 80% to 95%. Combined simvastatin + niacin was related to small increases in aspartate aminotransferase, creatine kinase, homocysteine, and insulin. Flushing was reported in 30%. Four of 80 discontinued niacin because of flushing.

## DISCUSSION

1. The rate of major clinical events was reduced by 90% in the simvastatin + niacin group.
2. Antioxidants provided no benefit. (Actually blunted the HDL-raising effect of simvastatin + niacin.)
3. The regression of stenosis in the simvastatin + niacin group was more than that expected from

statins alone.

4. Statins principally reduce LDL; niacin principally increases HDL. (*The decrease in LDL related to combined statin-niacin was somewhat greater than the average decrease reported from statin therapy alone. The increase in HDL was much more than usually reported from statins alone. RTJ*)
5. These findings apply to the many patients with coronary disease who have low HDL levels.
6. The results discourage use of antioxidants (which are frequently used based on unsupported perceptions) "Unless more compelling evidence appears, we see little justification for the use of antioxidant vitamins for the prevention of cardiovascular events."

## CONCLUSION

Compared with placebo, combined niacin-statin drug (simvastatin) provided marked clinical and angiographic benefits in patients with established coronary disease and low HDL levels. (Secondary prevention). The decrease in LDL related to combined statin-niacin was greater than the average decrease reported from statin therapy alone. The increase in HDL was much more than usually reported from statins alone. Antioxidants did not benefit. "Unless more compelling evidence appears, we see little justification for the use of antioxidant vitamins for the prevention of cardiovascular events."

NEJM November 29, 2001; 345: 1583-92 Original investigation, first author B Greg Brown, University of Washington School of Medicine, Seattle. [www.nejm.org](http://www.nejm.org)

Comment:

**1** I believe we should abandon the term "normal" in judging levels of lipids (as well as BP and other risk factors which have no distinct cut point between no risk and risk). Ie, if an LDL of 140 is considered "normal", then lowering it further should produce no benefit. But lowering LDL further does produce benefit. 140 cannot be termed "normal".

We will now proceed to consider if the combination is of value in *primary* prevention in patients with low HDL levels who do not respond adequately to statins alone.

. Tablets containing both drugs are coming on the market (*Advicor*). Niacin is relatively inexpensive. The problem will be acceptance of flushing. RTJ

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## **11-7 THE SAFETY OF INACTIVATED INFLUENZA VACCINE IN ADULTS AND CHILDREN WITH ASTHMA.**

Influenza makes people with asthma more susceptible to bronchoconstriction and prolonged declines in lung function. Influenza complicating asthma is a common reason for hospitalization of children.

Currently fewer than 10% of patients with asthma receive flu vaccine. It may be widely believed that it is not safe in these patients.

This study addressed the safety of flu vaccine.

Conclusion: Inactivated flu vaccine in patients with asthma was associated with the same adverse effects as placebo. It is safe.

## STUDY

1. Multicenter, randomized, double-blind, placebo-controlled, cross-over trial in over 2000 patients with asthma — age from 3 to 64.
2. For 2 weeks prior to study, all had stable asthma defined by absence of emergency room visits, hospitalizations, increased doses of corticosteroids, or urgent visits to a health care provider.
3. Randomized, cross over to:
  - A. Inactivated trivalent flu vaccine followed in 3 weeks with placebo injection, or
  - B. Placebo injection followed in 3 weeks with flu vaccine.
4. Primary outcome = an exacerbation of asthma in the 2 weeks following the injections. This was determined by measurement of peak expiratory flow rates, unscheduled visits to health care, use of asthma medications, and asthma-related absence from school or work.

## RESULTS

1. Frequency of exacerbations was similar in the 2 groups in the 2 weeks following the injections: 29% after placebo and 28% after flu.
2. Exacerbation rates were similar in subgroups. Only body aches, headache, and chills were, as expected, slightly more frequent after flu vaccine.

## DISCUSSION

1. "Influenza vaccine does not worsen asthma." Current guidelines for the immunization of patients with asthma are safe.
2. There was no difference in rates of exacerbation in the first 3 days after flu vaccine.
3. The high rate of spontaneous exacerbations, as well as the high rate of symptoms even after placebo shots, may explain the oft-held belief that immunization induces asthma.
4. Patients with more severe symptoms of asthma before either injection was given were more likely to experience an exacerbation after the injection. "Therefore we consider that inactivated influenza vaccine is safe in patients with more severe asthma."
5. The findings cannot be extrapolated to the cold-attenuated live influenza vaccines that may become available in the future. (Ie, the nasal vaccine.)
6. Fewer than 10% of patients with asthma are vaccinated against asthma. Programs that emphasize the importance of flu vaccine should be promoted.

## CONCLUSION

In a large diverse group of adults and children with asthma, vaccination was safe. Adverse effects were no more common after placebo shots than after flu shots.

Health care providers should urge patients with asthma to be immunized and thus reduce the morbidity associated with influenza.

NEJM November 22, 2001; 345: 1529-46 Original investigation by the American Lung Association Asthma Research Group. correspondence to Mario Castro, Washington University School of Medicine, St. Louis, MO

[www.nejm.org](http://www.nejm.org)

Comment:

All clinicians know that patients without asthma who receive the vaccine and within a few days develop symptoms will blame the vaccine. I used to tell patients I wished I had a dollar for every patient who told me "That flu shot gave me the flu". Asthma patients will also claim — "That flu shot worsened my asthma".

Primary care physicians have to defend use of the vaccine in asthma patients. Referring them to this study may help. RTJ

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### *Zaleplon (Sonata) a better hypnotic?*

#### **11-8 PYRAZOLOPYRIMIDINES: A New Drug Class**

Pharmacological therapy has an important role in the management of insomnia. The past 10 years have been marked by development of new hypnotic-sedative medications stimulated by the increased understanding of the role of gamma-amino butyric acid (**GABA**) an important neurotransmitter.

GABA is one of the most important inhibitory neurotransmitters in the central nervous system. Up to 50% of synapses use GABA as their transmitter.

Several new drug classes act by facilitating the effect of GABA. One, zaleplon (*Sonata*) is the subject of this review.

All modern hypnotic drugs, including benzodiazepines, interact with binding sites on a subunit of the GABA receptor. The receptor can be considered the hypnotic receptor (previously called the benzodiazepine receptor). Different drugs bind with different affinities to various subunits of the GABA receptor. This accounts for some of the variation in pharmacological response.

#### *Effects on sleep:*

Compared with placebo, zaleplon was associated with improvement in subjective sleep measures, including sleep latency, sleep duration, sleep quality. No significant adverse effects. No significant rebound insomnia when the drug was stopped. In elderly patients sleep latency was consistently reduced by the 10 mg dose by 35 minutes. The drug has a rapid elimination half life (half life ~ 1 hour). Sleep efficiency is improved over the first 4 hours. After this efficiency diminishes. Thus, in general, compared with placebo there are no significant differences with respect to overall sleep maintenance across 8 hours of sleep. For patients with difficulty initiating

sleep, zaleplon acts quickly in getting them to sleep, but will not typically extend sleep time. In patients with difficulty maintaining sleep, zaleplon may not help. For patients who easily get to sleep, but have trouble staying asleep, zaleplon if taken in the middle of the night might help to maintain sleep later during the night .

*Effects on psychomotor function and performance:*

Residual sedation is not generally seen with the recommended 5 mg (elderly) and 10 mg (non-elderly) doses, even when testing takes place immediately after administration. The absence of effects on psychomotor performance, even at peak plasma concentrations, seems to be a unique feature of zaleplon. No hangover effects are seen at the 20 mg dose. No significant memory impairment occurs at 5 or 10 mg doses.

*Side effects*

In studies up to 5 weeks, even with 20 mg doses, the frequency of side effects did not differ from placebo. Headache, GI upset, dizziness have been reported.

Zaleplon (*Sonata*) has many attributes of the ideal hypnotic agent — rapid absorption, rapid onset, adequate duration of action, minimum or no residual effect on daytime performance, and no evidence of pharmacological tolerance or withdrawal. "It provides another helpful option in the management of patients with insomnia."

Lancet November 10, 2001; 358: 1623-26 "New Drug Classes" commentary by C F P George, University of Western Ontario, London, Ontario, Canada. [www.thelancet.com](http://www.thelancet.com)

Comment:

Wholesale cost each capsule: 5 mg = \$1.81; 10 mg = \$2.23

This is a glowing recommendation. Primary care clinicians will judge if the benefits extend to individual patients. RTJ

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***Hope for prevention***

**11-9 ANTIOXIDANTS AND ZINC TO PREVENT PROGRESSION OF AGE-RELATED MACULAR DEGENERATION**

Observational and experimental data suggest that antioxidant and/or zinc supplementation may delay progression of age-related macular degeneration.(**ARMD**)

The Age-Related Eye-disease Study, sponsored by the National Eye Institute, was designed to evaluate the effect of supplements of high-dose vitamins C and E, beta-carotene, and zinc.

Conclusion: Patients at high risk of ARMD may benefit from a supplement of antioxidants and zinc.

**STUDY**

1. Multicenter, double-blind study entered over 3600 patients age 55 to 80. Divided into 4 groups having increasing severity of ARMD:

A. "No ARMD" — a few small drusen. (This group was eliminated from the study since the risk

of developing progression over 6 years was small ~ 1.3% in 5 years).

- B. "Early ARMD" — extensive small drusen, a few intermediate drusen, extensive intermediate drusen, or pigment abnormalities.
- C. "Intermediate ARMD" — large drusen, extensive intermediate drusen, non-central geographic atrophy
- D. "Advanced ARMD" — treatment of choroidal neovascularization ("wet ARMD") or photographic documentation of geographical atrophy involving the center of the macula, or with vision loss in one eye due to ARMD but not in the other, or extensive maculopathy from ARMD

(At least one eye had best-corrected vision to 20/32 or better. )

2. Randomized to daily administration of:

- 1. Vitamin C 500 mg; vitamin E 400 IU; beta carotene 15 mg. (Antioxidants)
- 2. Zinc oxide 80 mg and copper 2 mg as cupric oxide. (Zinc)
- 3. Antioxidants + zinc
- 4. Placebo.

3. Follow-up = 6 years for evidence of progression.

## RESULTS

- 1. Incidence of progression from early ARMD and intermediate ARMD to advanced ARMD was reduced significantly in the antioxidants + zinc group compared with placebo. Odds ratio = 0.66.
- 2. Odds ratios of developing advanced ARMD were reduced also for zinc alone (OR = 0.71) and antioxidants alone (OR = 0.76)
- 3. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in persons assigned to receive antioxidants + zinc.
- 4. No significant serious adverse events occurred.

## DISCUSSION

- 1. Compared with placebo, both 1) combination of antioxidants + zinc and 2) zinc alone reduced the odds of developing advanced ARMD in persons at risk of progression.
- 2. When only those participants with the greatest risk of progression to advanced ARMD and visual loss were considered, the combination of zinc + antioxidants had the most consistent treatment benefit, reducing the risk of development of moderate visual loss and development of advanced ARMD. (Odds ratio = 0.7)
- 3. "Based on the consistency of the data, and the general lack of any clinically significant serious adverse effects from these treatments, it is reasonable to conclude that persons found to have advanced ARMD in one eye of intermediate ARMD and who do not have contraindications should consider supplements with a combination of these antioxidants and zinc."
- 4. "This is the first treatment shown to slow the progression of ARMD and is a very important

advancement in this field, one that could delay or prevent vision loss in many patients."

5. The value of these supplements in persons at low risk remains uncertain.

## CONCLUSION

Persons older than 55 years should have dilated eye examinations to determine the risk of developing advanced ARMD.

Those with extensive intermediate size drusen, at least one large druse, non-central geographic atrophy in one or both eyes, or advanced ARMD or vision loss and without contraindications such as smoking (which may increase adverse effects of beta carotene) should consider taking a supplement of antioxidants plus zinc such as used in this study.

JAMA November 21, 2001; 286: 2466-68 Commentary by Lee M Jampol, Northwestern University Medical School, Chicago, ILL [www.jama.com](http://www.jama.com)

The original study "A Randomized Placebo-controlled Trial of High-dose Supplementation with Vitamin C, Beta-carotene, and Zinc for Age-related Macular Degeneration and Vision Loss" Archives of Ophthalmology Report No 8. 2001;119: 1417-36.

Comment:

Patients will be asking about this. Since the treatment is relatively inexpensive and safe, I believe clinicians will be willing to advise the supplements.

A recent study reported that statin drugs reduced risk of developing macular degeneration by about 90% Confirmation of both studies is urgently needed.

"Risk of macular degeneration in users of statins" BMJ August 18, 2001; 323: 375-76

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## 11-10 LEGUME CONSUMPTION AND RISK OF CORONARY HEART DISEASE IN US MEN AND WOMEN

*(My dictionary defines legumes as a plant bearing pods, such as peas or beans, which split into two halves with the seeds attached to the lower edge of one of the valves. RTJ )*

Legumes are high in bean protein and water-soluble fiber. Soluble fiber has been shown to reduce total and LDL-cholesterol levels and to reduce insulin resistance. They are also rich in minerals such as potassium, magnesium and calcium, and low in sodium, factors which also have been associated with reduced risk of cardiovascular disease.

Randomized trials have shown that substituting protein from vegetable sources for protein of animal sources reduces cholesterol.

This study assessed the relation between consumption of legumes and coronary heart disease.

Conclusion: Legume intake provided a significant protective effect.

## STUDY

1. Prospective cohort study Entered over 9500 men and women who participated in the First National Health and Nutrition Examination Survey (NHEFS). All were free of known cardiovascular disease at baseline.
2. Estimated frequency of legume intake by a 3-month food frequency questionnaire. Foods included dry beans, peas, pinto beans, black-eyed peas; and peanuts and peanut butter.
3. Obtained incidence of coronary heart disease (**CHD**) and cardiovascular disease (**CVD**) from medical records and death certificates.
4. Follow-up = an average of 19 years.

## RESULTS

1. Over 19 years over 1800 incident cases of CHD and over 3600 incident cases of CVD were documented.
2. Legume consumption was significantly and inversely associated with risk of CHD and CVD after adjustment for established risk factors. Consumption of legumes 4 times a week or more, compared with less than once a week, was associated with a 22% lowering of CHD and a 11% lowering of CVD. However, significant benefit was limited to those over age 60 at baseline. In this older group, those with an intake of at least 4 times weekly had a 38% lower risk of CHD and a 27% lower risk of CVD.
3. Persons with more frequent legume intake had less hypertension, less hypercholesterolemia, less diabetes, and lower body mass index than those consuming legumes less often.

## DISCUSSION

1. "Our study found a strong and independent inverse association between dietary intake of legumes and risk of CHD in a representative sample of non-institutionalized adult US population." The findings are highly generalizable.
2. "Increasing legume intake may be an important part of dietary interventions to reduce heart disease."

## CONCLUSION

A significant benefit in reducing incidence of cardiovascular disease was associated with increased legume consumption of at least 4 servings weekly.

Archives Int Med November 26, 2001; 161; 2573-78 Original investigation by the NHANES I

**[www.archinternmed.com](http://www.archinternmed.com)**

Epidemiological Follow-up Study, first author Lydia A Bazzano, Tulane University School of Public Health and Tropical Medicine, New Orleans, LA.

Comment:

This is another study indicating — "Eat your fruits and vegetables".

The inclusion of peanuts suggested to me that peanuts may have a dual protective effect, first as a member of the nut family and second as a member of the legume family. Of course, peanut butter must not be hydrogenated. (Ie, the oil should not be converted to trans fat.) RTJ

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*More evidence of benefit associated with lowering homocysteine levels*

**11-11 DECREASED RATE OF CORONARY RESTENOSIS AFTER LOWERING OF PLASMA HOMOCYSTEINE LEVELS.**

Restenosis after percutaneous coronary angioplasty (**PTCA**) remains an important limitation of the procedure.

Homocysteine level is an important predictor of cardiovascular risk. It correlates with severity of coronary artery disease. Patients with low levels of homocysteine have lower rates of coronary restenosis.

Since plasma homocysteine can be lowered by up to 30% with a daily dose of 500 ug of folic acid in combination with vitamin B12 and pyridoxine, the investigators hypothesized that vitamin therapy would decrease rate of restenosis after PTCA.

Conclusion: Vitamin therapy was associated with a significant reduction in homocysteine levels and a decrease in the rate of restenosis after PTCA.

**STUDY**

1. Prospective, double-blind, placebo-controlled trial entered over 200 patients with coronary disease.

All underwent a successful PTCA. (A secondary prevention trial.)

2. Randomized to:

A. Vitamin supplementation regimen: folic acid — 400ug; pyridoxine 10 mg; and vitamin B12 400 ug daily. (*My vitamin supplement contains 400 ug of folic acid, 2 mg B6, and 6 ug of B12. Additional supplementation is needed to reach the levels of B6 and B12 used in the study. RTJ*)

B. Placebo

3. Followed at 6 months by repeat coronary angiography.

4. Primary end point = restenosis.

**RESULTS**

1. The vitamin treatment was associated with a significantly lowered plasma homocysteine level (from 11 to 7 umol/L).

2. In the treatment group at 6 months, luminal diameter was larger and degree of stenosis lower.

3. Rate of restenosis = 37% in the placebo group vs 20% in the folate group. Need for revascularization: placebo = 22%; vitamin group = 11% [NNT(benefit one patient over 6 months) = 9]

**DISCUSSION**

1. The study provides evidence that folate, B12, B6 treatment, lowers homocysteine levels and is

associated with a significantly reduced rate of restenosis after PTCA.

2. The folate combination is inexpensive and safe.

## CONCLUSION

Treatment with a combination of folic acid, vitamin B12 and pyridoxine (B6) was associated with a significant reduction in the rate of restenosis after PTCA.

NEJM November 29, 2001; 345: 1593-600 Original investigation, first author Guido Schnyder, Swiss Cardiovascular Center, University Hospital, Berne Switzerland. [www.nejm.org](http://www.nejm.org)

Comment:

An association between homocysteine and atherosclerosis was discovered years ago in patients with homozygous homocysteinemia.

This study does not directly concern primary care clinicians. I abstracted the study because it strengthens the putative association between homocysteine and atherosclerosis. It points out that treatment which will lower levels is readily available, safe, effective, and inexpensive.

Primary care clinicians would be much more likely to use still unsubstantiated therapy and accept more uncertainty if the drugs prescribed are inexpensive and cause no adverse effects. The use of the vitamin combination is a good example. I believe it gives a boost to prescribing the vitamin combination for primary prevention. RTJ

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*This simplifies secondary prevention*

## **11-12 A COMPARISON OF WARFARIN AND ASPIRIN FOR THE PREVENTION OF RECURRENT ISCHEMIC STROKE.**

Warfarin is standard therapy for prevention of cardioembolic stroke in patients with atrial fibrillation.

Thus far, no trial has determined whether anticoagulation with warfarin is superior to the antiplatelet activity of aspirin in prevention of non-cardiac forms of ischemic stroke.

This study asks: Is warfarin superior to aspirin in *secondary* prevention of non-cardiac stroke?

Conclusion: No

## STUDY

1. Double-blind randomized trial compared warfarin with aspirin in over 2000 patients (mean age = 63).

All had a non-cardiac ischemic stroke within 30 days of randomization. (Those with atrial fibrillation were excluded.)

2. Randomized to: 1) warfarin to achieve an INR of 1.4 to 2.8, or 2) aspirin 325 mg daily.

3. Primary end point = recurrent ischemic stroke or death from any cause. Follow-up = 2 years.

## RESULTS

1. No significant differences in outcomes between groups. Primary end point occurred in 18% of warfarin group vs 16% in the aspirin group.
2. Rates of major hemorrhage were low— 2.2 per 100 patient-years in the warfarin group vs 1.49 in the aspirin group
3. No difference in time to primary end point.

## DISCUSSION

1. There was no significant difference between treatment with warfarin vs aspirin in prevention of recurrent non-cardiac stroke or death, or the occurrence of serious adverse effects.
2. Actually, warfarin was associated with a non-significant 13% higher increase in risk of recurrent stroke.
3. Aspirin, either alone, or in combination with some other antiplatelet agent, appears to be a well-justified choice for the prevention of recurrent ischemic stroke.

## CONCLUSION

Over a 2 year period, there was no difference between aspirin and warfarin in prevention of recurrent non-cardiac stroke or death.

NEJM November 15, 2001; 345: 1444-51 Original investigation by the "Warfarin-Aspirin Recurrent Stroke Study Group", first author J P Mohr, Columbia Presbyterian Medical Center, New York. [www.nejm.org](http://www.nejm.org)

### Comment

Although the authors concluded that both warfarin and aspirin are reasonable therapeutic alternatives for this purpose, aspirin is favored because of the low cost and convenience, and also perhaps because of slightly greater effectiveness and safety. RTJ

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### ***Therapeutic Change After 50 Years Of Anticoagulant Use For Stroke Prevention***

#### **ORAL ANTICOAGULANT THERAPY FOR THE PREVENTION OF STROKE.**

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

Select patients with an ischemic stroke in the territory of a stenotic carotid artery are benefited by endarterectomy. Some with atrial fibrillation are benefited by warfarin therapy.

More than 2 out of 3 patients with a first ischemic stroke have no identified cardiac source and are not candidates for carotid endarterectomy. Antiplatelet (aspirin) therapy reduces rate of recurrent stroke by 30%. Nevertheless, under the best of conditions the rate of recurrence of non-cardiac stroke is up to 7% yearly. Recurrent stroke accounts for one third of all strokes. "We need to do better."

"For more than 50 years, physicians have prescribed warfarin for patients with non-cardioembolic stroke in the hope that subsequent strokes could be prevented. This treatment was based on a mixture of clinical experience,

observational studies, and inferences about the pathophysiology of stroke. Aspirin has an established benefit in preventing recurrent stroke. So also for warfarin. (The outcomes in the trial were statistically equal.) The evidence does not support use of oral anticoagulant therapy at any international normalized ratio as a general strategy for prevention of recurrent non-cardioembolic stroke. It provides no benefit over aspirin. It is expensive and more difficult to manage. It is unlikely that the low incidence of hemorrhage achieved in the trial can be matched in routine clinical practice.

"Aspirin alone, or in combination with some other antiplatelet agents appears to be a well-justified choice for the prevention of recurrent ischemic stroke"

NEJM November 15, 2001; 345: 1493 Editorial by William J Powers, Washington University School of Medicine, ST. Louis, MO. [www.nejm.org](http://www.nejm.org)

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**REFERENCE ARTICLE *Hypochondriacs have been described as having "illness as a way of life"***

**11-13 THE PATIENT WITH HYPOCHONDRIASIS**

Hypochondriasis is chronic and disabling. Disability and impairment of role functioning may be as severe as the dysfunction which accompanies major mood and anxiety disorders and many chronic medical conditions.

Hypochondriasis is found in about 5% of general medical outpatients.

Hypochondriasis is refractory to standard medical management. Indeed, treatment often leads to complications, side effects, and new symptoms. Patients are difficult to reassure. Their treatment is time consuming. Physicians often develop antipathy toward them and find them difficult and frustrating to treat. Indeed, the combination of anger and frustration experienced by the physician is often a signal that the patient has hypochondriasis.

Patients with hypochondriasis are preoccupied with the fear or belief that they have a serious, undiagnosed, disease. Their concern derives from a misinterpretation of benign physical sensations as evidence of serious illness. It persists despite reassurance. Diagnosis requires that the symptoms cause significant distress or functional impairment.

These patients are reluctant to acknowledge the role of psychosocial factors in causing their symptoms

Somatization, a related phenomenon, refers more generally to the patient's tendency to focus on the somatic manifestations of emotional distress and to present with somatic symptoms that have no demonstrable organic basis. Patients with hypochondriasis are a subgroup of patients who somatize — namely those whose medically unexplained symptoms are accompanied by an unshakable conviction that they have a serious disease. Overlap exists.

Hypochondriacal concern spans a spectrum from mild, fleeting worry to persistent and incapacitating dread. The disability is unresponsive to repeated reassurance and negative diagnostic evaluations. It is refractory to standard symptomatic treatments. Bodily symptoms (often normal physiological symptoms or benign self-limited ailments) are misinterpreted as serious, and are accompanied by profound anxiety. Hypochondriacs have been described as having "illness as a way of life"

It should be emphasized that they are not malingering or fabricating their symptoms.

Patients with hypochondriasis have a characteristically paradoxical history of medical care. They have high rates of visits, tests, specialty consultations, and surgical procedures. And high health costs. They find their care frustrating and unsatisfactory. They feel ignored. They may respond to appropriate reassurance with anger rather than relief.

So, what to do?

Cognitive-behavioral therapy:

Is promising. However, studies of effectiveness tend to be small and lack controls.

It requires a special program with multiple sessions, and trained therapists.

Pharmacotherapy:

There is good evidence that vigorous treatment of psychiatric disorders that frequently co-exist are responsive to drugs. Drug treatment may help resolve hypochondriacal symptoms associated with major depression, panic disorder, and obsessive-compulsive disorder. (*See table 2 p 1397*)

Relation to the doctor:

Brief, and frequent regular visits should be advised rather than "as needed" visits. Diagnostic procedures, surgery, lab tests, consultations, should be performed only when clearly indicated. Explicitly acknowledge that the patient's symptoms are real and not imaginary or fabricated.

Successful long-term management requires a durable and trusting doctor-patient relationship in which access to the doctor is not predicated on an as-needed basis. Try not to vary the frequency of appointments when the number or severity of symptoms increases or decreases. At the same time be alert to the possibility of an organic basis. Regular visits, careful physical examinations, and attentive listening are useful approaches to therapy. Search for evidence of other psychiatric disorders — major depression, panic disorders, and obsessive-compulsive disorder. Treatment of the co-existent psychiatric disorder typically ameliorates hypochondriacal symptoms.

Benign remedies:

Lotions, vitamins, elastic bandages, and heating pads can be helpful because they provide tangible evidence of the patient's distress and the doctor's ongoing interest.

Simply reassuring these patients that there is "nothing wrong" contradicts their own experience. It may be helpful to explain that they are exceptionally sensitive to normal bodily sensations and may misinterpret them as serious illness. Any such explanation must be coupled with the explicit assurance that the physician understands that such symptoms are not "imaginary".

Patients with hypochondriasis tend to resist referral to a psychiatrist. They may interpret a referral to mean that they are imagining or fabricating symptoms. Some may acknowledge that they may have emotional distress for which they may accept psychiatric help while insisting that it bears no causal relationship to their somatic symptoms.

Although there is no definitive therapy, physicians can effectively care for patients with hypochondriasis by acknowledging that somatic symptoms without a medical basis can be as distressing as those resulting from demonstrable disease. The goal of treatment should be to improve coping with symptoms rather than their elimination, as in the management of chronic physical illness. This approach minimizes the frustration of both the patient and the physician.

NEJM November 8, 2001; 345: 1395-99 Commentary by Arthur J Barsky, Brigham and Women's Hospital, Boston, Mass. [www.nejm.org](http://www.nejm.org)

Comment:

This article is one of a series, "Clinical Practice", which highlight common clinical problems, evidence supporting various treatment strategies, and the author's recommendations. RTJ

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## 11-14 HORMONE REPLACEMENT THERAPY AND DRY EYE SYNDROME

Some research suggests that postmenopausal hormone replacement therapy (**HRT**) may have detrimental effects on the tear film and could influence the development of dry eye syndrome. (**DES**)

This study asked— Does HRT increase incidence of DES?

Conclusion: Yes it does.

### STUDY

1. At baseline, a large cohort of women (25 000) provided information about use of HRT.
2. Continued inquiry about HRT at 12 and 36 months.
3. Inquired about dry eye syndrome at 48 months.

### RESULTS

1. Prevalence of DYS at 4th year:
  - Women who had never used HRT — 5.9%.
  - Women who had used estrogen alone — 9.1% (NNT harm = 31)
  - Women who had used estrogen-progesterone — 6.7% (NNT harm = 125)
2. Each 3-year use was associated with a significant 15% elevation in risk .

### DISCUSSION

1. Most epidemiological studies conclude that dry eye syndrome is more common in women.
2. Postmenopausal women who used HRT had a higher prevalence of DES than never users.
3. Estrogen-alone users had a higher prevalence of DES than users of combined estrogen-progesterone. (+ 69% vs +29% compared with never-users.)
4. The longer the use, the higher the risk.

5. Postmenopausal women who never used HRT had the same prevalence as premenopausal women.
6. Estrogens have an inhibitory effect on sebaceous glands. The authors speculate that estrogens have a drying effect on the meibomian<sup>1</sup> and lacrimal glands.

## CONCLUSION

Postmenopausal women who used HRT had a higher prevalence of dry eye syndrome compared with never-users.

JAMA November 7, 2001; 286: 2114-19 Original investigation, first author Debra A Schaumberg, Brigham and Women's Hospital, Boston, Mass. [www.jama.com](http://www.jama.com)

**1** The meibomian glands (tarsal glands) are sebaceous glands embedded in the tarsal plate of each eyelid. They discharge at the edge of the lid near the posterior border. Their secretions create a lipid barrier along the margin of the eyelids which prevents the normal watery secretions of the conjunctival sac from spilling over when the eye is open.

Comment:

This was my introduction to this nexus. For women who rely on HRT are on estrogen alone and develop DES, would it not be reasonable to add progesterone? The NNT(harm) by estrogen-progestin is much higher. Ie, fewer women develop DES than estrogen-alone users. RTJ

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## **11-15 A SIMPLE RISK INDEX FOR RAPID INITIAL TRIAGE OF PATIENTS WITH ST-ELEVATION MYOCARDIAL INFARCTION**

Rapid, effective triage is essential for emergency cardiac care of patients with ST elevation myocardial infarction (**MI**). In a growing number of emergency medical systems, decisions regarding triage to tertiary centers are now made outside the hospital, guided by rapid risk assessment. In patients who present directly to the emergency department, immediate assessment of risk is equally important.

Increasing age, low systolic BP and rapid heart rate have been associated with increased risk.

This study developed and assessed a combination of these immediately available clinical factors in assessing risk of mortality from acute MI.

Conclusion: A simple combination of increasing age, increasing heart rate and decreasing systolic BP predicted mortality.

## STUDY

1. Developed and assessed a risk index on the basis of observed risk relations among over 13 000 patients with ST-elevation MI.
2. The risk index included age, systolic BP and heart rate to develop a formula to predict mortality over 30 days.

3. The formula -- heart rate x (age/10)<sup>2</sup> / systolic BP.
4. Divided the cohort into quintiles for convenient clinical use.

RESULTS

1. The risk index was a strong and independent predictor of mortality.
2. The index was also a robust predictor of very early events, including death within 24 hours.

Risk index (quintiles)	Death in 24 hours	Death within 30 days
< 12	0.2%	1%
12-17	0.4%	2%
18-22	1%	3%
23-30	2.4%	8%
> 30	7%	17%

DISCUSSION

1. A combination of the 3 strongest clinical predictors of mortality risk into a single risk index provided an effective and simple tool for rapid risk assessment.
2. Pre-hospital ECG and assessment of eligibility for reperfusion therapy has been shown to reduce time to treatment and could be associated with improved survival.

CONCLUSION

A simple risk index based on age, heart rate, and systolic BP captured most of the information from more complex tools. Risk rose sharply after age 60, with a pulse rate of above 80, and when systolic BP fell below 120. The index is likely to be useful in rapid triage of patients with ST-elevation acute MI.

The formula -- heart rate x (age/10)<sup>2</sup> / systolic BP.

Lancet November 10, 2001; 358: 1571-75 Original investigation, first author David A Morrow, Brigham and Women's Hospital, Boston Mass. [www.thelancet.com](http://www.thelancet.com)

Comment:

This assessment could be a useful indicator for immediate use of a new bolus fibrinolytic agent at the primary encounter site. Primary care clinicians may do just as well in assessing risk by empirically combining pulse rate, age, and systolic BP. RTJ

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*An addition to the many*

**11-16 CHOOSING A PARENTERAL ANTICOAGULANT AGENT**

There has been an explosion of the number of available parenteral anticoagulant drugs. There are currently 4 low-molecular-weight heparins (LMWH), one heparinoid, two hirudin derivatives, and one direct thrombin

inhibitor. (See list p 1341) All have been approved for use and have defined roles in patients requiring anticoagulation.

This issue on NEJM introduces another — fondaparinux, a direct factor Xa inhibitor.

Fondaparinux is derived from the activated factor X (Xa) binding moiety of unfractionated heparin.

Two studies <sup>1,2</sup> report that once-daily treatment initiated early in the postoperative period was more effective than LMWH in preventing venous thromboembolism after hip and knee surgery.

Fondaparinux has been approved by the FDA for prevention of thromboembolism after orthopedic surgery. (Arixtra)

NEJM November 1, 2001; 345: 1340-41 Editorial by David L Diuguid, College of Physicians and Surgeons of Columbia University, New York. [www.nejm.org](http://www.nejm.org)

1 "Fondaparinux Compared with Enoxiparin for the Prevention of Venous Thromboembolism after Hip-Fracture Surgery" NEJM November 1, 2001; 345: 1298-304

2 "Fondaparinux Compared with Enoxiparin for the Prevention of Venous Thromboembolism after Elective Major Knee Surgery" NEJM November 1, 2001; 345: 2001-10

Comment:

I abstracted this article to inform primary care clinicians about the rapid additions to anticoagulant therapy. We must rely on continued advice from the experts about the best-use.

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## **11-17 NONSTEROIDAL ANTIINFLAMMATORY DRUGS AND THE RISK OF ALZHEIMER'S DISEASE**

An inflammatory response which includes a local cytokine response and activation of the complement cascade is one of the neuropathologic features of Alzheimer's disease (**AD**). This inflammatory response may damage neurons and exacerbate the pathologic process underlying the disease.

NSAIDs may influence this inflammatory response and help prevent the disease. Observational studies, however, have yielded inconsistent results.

This long-term study was based on the strength of the Netherland's computerized pharmacy records which are virtually complete sources of information on the delivery of drugs.

Conclusion: The long-term use of NSAIDs may be protective.

### **STUDY**

1. Prospective, population-based cohort study of almost 7000 patients over age 55. All were free of dementia at baseline.
2. Estimated risk of AD in relation to use of NSAIDs.
3. Sixteen NSAIDs were documented, the most common being diclofenac, ibuprofen, and naproxin.
4. Determined four categories of use: non-use; short-term use (1 month or less); intermediate-term use

( one months to 2 years of cumulative use); and over 2 years of cumulative use.

5. Determined incidence of dementia over a 7-year follow-up.

## RESULTS

1. Dementia occurred in 5.6% of patients:

AD	4.2%
Vascular dementia	0.8%
Other	0.6%

2. Relative risk of AD according to length of use compared with no use:

Less than 1 month	0.98
One month to 2 years	0.8
Over 2 years	0.2 (Only 3 of 233 patients developed AD.)

3. Risk did not vary with age.

4. No reduction in incidence of vascular dementia.

## DISCUSSION

1. "In this prospective, population-based study, we found a significantly reduced risk of Alzheimer's disease in subjects who had taken NSAIDs for a cumulative period of 24 months or more."

2. The results are compatible with the hypothesis that inflammatory mechanisms may play a part in AD.

3. The study emphasizes that the information about NSAID use was taken from pharmacy records which in the Netherlands are very complete.

4. At baseline a number of patients were already taking NSAIDs. Thus the period of use may have been longer.

## CONCLUSION

Long-term use of NSAIDs may have a beneficial effect in preventing AD. "Primary-prevention trials should be undertaken to confirm this finding and show whether the benefits of such therapy outweigh the risks."

NEJM November 22, 2001; 345: 1515-21 Original investigation, first author Bas A in'T Veld, Erasmus Medical Center, Rotterdam, Netherlands. [www.nejm.org](http://www.nejm.org)

Comment:

Should primary care clinicians prescribe NSAIDs for this purpose? I doubt many would until more definitive results are available. The report is provocative. Follow-up studies are essential.

Other connections to Alzheimer's are emerging: statin drugs and cognitive stimulating activities have been reported to lower risk. Elevated homocysteine levels have been reported to be related to increased risk. RTJ



