

**PRACTICAL POINTERS  
FOR  
PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

**AUGUST 2000**

**THE ART OF LISTENING TO THE PATIENT**

**LOW-DOSE BETA-BLOCKERS TO TREAT HEART FAILURE**

**ALENDRONATE TO TREAT OSEOPOROSIS IN OLDER MEN**

**CARDIOVASCULAR COMPLICATIONS OF TYPE 2 DIABETES PARALLEL GLYCEMIA.**

**MICRO-VASCULAR COMPLICATIONS OF TYPE 2 DIABETES PARALLEL SYSTOLIC BP**

**TO AVOID COMPLICATIONS CONTROL HbA1c TO 6% AND SYSTOLIC BP BELOW 140**

**STATIN THERAPY REDUCES RISK OF STROKE (SECONDARY PREVENTION STUDY)**

**CARDIOVASCULAR RISK FACTORS ARE ASSOCIATED WITH CAROTID ATHEROSCLEROSIS**

**ESTROGENS DID NOT SLOW ATHEROSCLEROSIS OF THE CORONARY ARTERIES**

**EVIDENCE THAT ESTROGEN ACCOUNTS FOR SOME OF THE DECLINE IN CHD**

**COGNITIVE DECLINE RELATED TO NON-PROTEIN BOUND ESTROGEN**

**A PROGNOSTIC SCORE FOR UNSTABLE ANGINA**

**STOPPING SMOKING IN MIDDLE-AGE REDUCES RISK OF LUNG CANCER.**

**OMEPRAZOLE FOR EROSIIVE ESOPHAGITIS IS SAFE AND EFFECTIVE LONG-TERM**

**HOW TO PREDICT OUTCOME IN PATIENTS WITH SEVERE AORTIC STENOSIS**

**IV OMEPRAZOLE TO REDUCE RISK OF RE-BLEEDING PEPTIC ULCER**

**ARE ZINC LOZENGES EFFECTIVE IN TREATING COLDS?**

**CAN YOU BLIND THE TASTE OF ZINC LOZENGES?**

**A SIMPLE, RAPID TEST FOR FALCIPARUM MALARIA..**

**A NEW TREATMENT FOR DIARRHEA IN CHILDREN**

**RECOMMENDED READING**

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# HIGHLIGHTS AUGUST 2000

## **8-1 A STUDY OF PATIENT CLUES AND PHYSICIAN RESPONSES IN PRIMARY CARE AND SURGICAL SETTINGS.**

A clue is a direct or indirect comment that provides information about any aspect of a patient's feelings or life circumstances. Clues offer a glimpse into the inner world of patients and create an opportunity for empathy and personal connection. By exploring the meaning of these clues for the patient, physicians can deepen the therapeutic relationship and potentially enhance clinical outcomes.

Physicians often by-pass these clues, missing potential opportunities to strengthen trust and the patient-physician relationship.

Physicians can learn to modify their communication style.

## **8-2 RATE OF HEART FAILURE AND 1-YEAR SURVIVAL FOR OLDER PEOPLE RECEIVING LOW-DOSE BETA-BLOCKER THERAPY AFTER MYOCARDIAL INFARCTION**

Beta-blockers are standard therapy for patients with heart failure. Compared with high-dose beta-blocker therapy, low-dose treatment was associated with a lower rate of hospital admission for heart failure. Patients receiving a low dose had a similar 1-year survival benefit.

A low dose would be atenolol 25 mg daily.

The potential survival benefit of low-dose BBs may encourage physicians to use these drugs in frail elderly people for whom BBs might not be prescribed. The group receiving low-dose BB included those who were older and most frail. This group may receive the most benefit from low-dose therapy.

## **8-3 ALENDRONATE FOR THE TREATMENT OF OSTEOPOROSIS IN MEN.**

In men with osteoporosis, alendronate significantly increased BMD and helped prevent vertebral fractures and decreases in height.

## **8-4 ASSOCIATION OF GLYCEMIA WITH MACROVASCULAR AND MICROVASCULAR COMPLICATIONS OF TYPE 2 DIABETES (UKPDS 35)**

Cardiovascular and cerebrovascular disease account for more than 50% of all mortality in diabetic populations. The data suggest that any improvement in glycemic control across the diabetic range is likely to reduce the risk of cardiovascular complications. Even a modest reduction in glycemia has the potential to prevent deaths from *macro*-vascular complications related to diabetes.

Glycemia is a risk factor for *macro*-vascular complications as well as *micro*-vascular complications.

## **8-5 ASSOCIATION OF SYSTOLIC BLOOD PRESSURE WITH MACROVASCULAR AND MICROVASCULAR COMPLICATIONS OF TYPE 2 DIABETES. (UKPDS 36)**

This is the converse of the preceding investigation. The risk of *macro*-vascular complications related to systolic BP is well established. This study provides evidence that *micro*-vascular complications (renal retinal, and peripheral nerve) may also be related to systolic BP.

## **8-6 CONTROLLING GLUCOSE AND BLOOD PRESSURE IN TYPE 2 DIABETES.**

The clinical message is clear and important. To avoid complications control the HbA1c as close to 6% as possible and the systolic BP as low as possible. We must ask whether treatment to lower raised glucose should be started much earlier. Perhaps impaired glucose tolerance should be an indication for treatment.

## **8-7 PRAVASTATIN THERAPY AND THE RISK OF STROKE**

Therapy with the statin drug, pravastatin, was associated with a reduction in the rate of stroke as well as the rate of coronary disease in patients with established coronary disease. (Secondary prevention.)

## **8-8 STRONG AND SIGNIFICANT RELATIONSHIPS BETWEEN AGGREGATION OF MAJOR CORONARY RISK FACTORS AND THE ACCELERATION OF CAROTID ATHEROSCLEROSIS IN THE GENERAL POPULATION OF A JAPANESE CITY.**

There was a strong relationship between the aggregation of 3 major risk factors (hypertension, high cholesterol, and smoking) and acceleration of progression of carotid atherosclerosis. Intimal-medial thickness (IMT) of the carotid arteries is a good indicator of the presence and extent of coronary artery disease. "Our data suggest that it is possible to infer non-invasively and correctly the extent of coronary atherosclerosis on the basis of carotid atherosclerosis."

Studies indicate that as the IMT increases, the risk of myocardial infarction increases.

## **8-9 EFFECTS OF ESTROGEN REPLACEMENT ON THE PROGRESSION OF CORONARY-ARTERY ATHEROSCLEROSIS**

Three years of treatment with estrogen and estrogen-progestin did not slow progression of coronary atherosclerosis in postmenopausal women who had established disease at baseline.

"These results suggest that such women should not use estrogen replacement with an expectation of cardiovascular benefit."

"Estrogen therapy may still be effective for the *primary* prevention of coronary heart disease, but this has not yet been verified."

"Estrogen therapy may still be effective for the *primary* prevention of coronary heart disease, but this has not yet been verified."

## **8-10 TRENDS IN THE INCIDENCE OF CORONARY HEART DISEASE AND CHANGES IN DIET AND LIFESTYLE IN WOMEN**

There was a substantial decline in incidence of CHD from 1980 to 1995 among women in the Nurses' health Study. Reductions in smoking, improvement in diet, and increase in HRT accounted for much of the improvement.

Increase in the incidence of obesity appears to have prevented a further improvement.

These factors are important in primary prevention of CHD.

#### **8-11 COGNITIVE DECLINE IN WOMEN IN RELATION TO NON-PROTEIN BOUND OESTRADIOL CONCENTRATIONS**

Older women with high concentrations of non-protein-bound and bioavailable estradiol were less likely to develop cognitive dysfunction than women with low concentrations.

#### **8-12 THE TIMI RISK SCORE FOR UNSTABLE ANGINA/NON-ST ELEVATION MI**

In patients with UA/NSTEMI the TIMI risk score of 7 clinical variables is a simple prognostic scheme that categorizes a patient's risk of death and ischemic events. It provides a basis for therapeutic decision-making. The low-molecular-weight heparin enoxiparin was more beneficial than unfractionated heparin.

#### **8-13 SMOKING, SMOKING CESSATION AND LUNG CANCER IN THE UK SINCE 1950**

Smokers who stop even well into middle age avoid most of their subsequent risk of lung cancer. Stopping before middle age avoids more than 90% of the risk attributable to tobacco.

Mortality throughout the first half of the 21st century could be substantially reduced by current smokers giving up the habit.

Young persons who begin to smoke now will henceforth become statistics in the middle and second half of the century.

The good news — it's never too late to stop.

#### **8-14 LONG-TERM SAFETY AND EFFICACY ON OMEPRAZOLE IN GASTRO-OESOPHAGEAL REFLUX DISEASE.**

Long-term therapy was safe and effective. Patients with erosive esophagitis did well over 6 years.

#### **8-15 PREDICTORS OF OUTCOME IN SEVERE, ASYMPTOMATIC AORTIC STENOSIS**

In asymptomatic patients with AS, it appears relatively safe to delay surgery until symptoms develop, However, outcomes vary widely. The presence of moderate or severe calcification, together with a rapid increase in aortic-jet velocity, identifies patients with a very poor prognosis. These patients should be considered for early valve replacement rather than have surgery delayed until symptoms develop.

#### **8-16 AORTIC STENOSIS — LISTEN TO THE PATIENT, LOOK AT THE VALVE**

The optimum time to perform valve replacement is as soon as symptoms begin. There is substantial variation in the degree of stenosis associated with the onset of symptoms. The presence of moderate to severe calcification and increasing aortic-jet velocity over time are strong predictors of outcomes.

#### **8-17 EFFECT OF INTRAVENOUS OMEPRAZOLE ON RECURRENT BLEEDING AFTER ENDOSCOPIC TREATMENT OF BLEEDING PEPTIC ULCERS**

After endoscopic treatment of active bleeding from a peptic ulcer, high-dose omeprazole given iv substantially reduced risk of rebleeding.

#### **8-18 DURATION OF SYMPTOMS AND PLASMA CYTOKINE LEVELS IN PATIENTS WITH THE COMMON COLD TREATED WITH ZINC ACETATE**

Treatment with zinc lozenges was associated with reduction in the duration and severity of symptoms of the common cold.

#### **8-19 LESSONS LEARNED FROM ATTEMPTS TO ESTABLISH THE BLIND IN PLACEBO-CONTROLLED TRIALS OF ZINC FOR THE COMMON COLD**

The editorialist remains unconvinced. He suspects that the placebo and the zinc had detectable differences, and that the blind was not completely established.

#### **8-20 RAPID DIAGNOSIS OF FALCIPARUM MALARIA BY USING THE PARASIGHT F TEST IN TRAVELERS RETURNING TO THE UNITED KINGDOM**

This simple diagnostic strip test detects a water soluble antigen (histidine rich protein 2) produced by blood stages of *P falciparum* . The test is simple and rapid. And has high predictive values.

#### **8-21 RACECADOTRIL IN THE TREATMENT OF ACUTE WATERY DIARRHEA IN CHILDREN.**

A new enkephalinase inhibitor reduces symptoms of diarrhea in children.

#### **RECOMMENDED READING**

##### **8-1 A STUDY OF PATIENT CLUES AND PHYSICIAN RESPONSES IN PRIMARY CARE AND SURGICAL SETTINGS.**

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### **RECOMMENDED READING**

## **8-1 A STUDY OF PATIENT CLUES AND PHYSICIAN RESPONSES IN PRIMARY CARE AND SURGICAL SETTINGS.**

Patients often present clues which offer opportunities for understanding their lives and emotions. They may not verbalize their anxieties, but raise these issues indirectly by offering clues or hints ("empathic opportunities") about their concerns.

A clue is a direct or indirect comment that provides information about any aspect of a patient's feelings or life circumstances. Clues offer a glimpse into the inner world of patients and create an opportunity for empathy and personal connection. By exploring the meaning of these clues for the patient, physicians can deepen the therapeutic relationship and potentially enhance clinical outcomes.

Patients view medical experiences as intertwined with the issues of their everyday lives. Not surprisingly then, patients expect physicians to go beyond merely attending to their biomedical needs. Many patients view their physicians as individuals whom they can trust with their most intimate information — including the stresses of their daily lives and their personal worries.

This study assessed how patients present clues and how physicians respond to these clues in routine, primary care practice.

Conclusion: Patients presented clues frequently. Physicians responded poorly.

### **STUDY**

1. Descriptive, qualitative study entered over 100 randomly selected office visits to 54 primary care physicians. (Also included a group of surgeons. I omitted these results. They were similar.)
2. Audiotaped each visit.
3. Assessed frequency of presentation of clues, emotional and social content of clues, and nature of physician responses.
4. Broadly categorized physician responses as positive or missed opportunities.
  - A. Positive responses included: direct acknowledgement of the patient's feeling; encouragement, praise, or reassurance; and supportive statements.
  - B. Missed opportunities included: inadequate acknowledgment; inappropriate humor; denials of concerns; and termination or redirection of the discussion. (*See text.*)

### **RESULTS**

1. One half of all visits included one or more clues. During visits with clues, the mean number of clues per visit was 2.6.
2. Patients initiated most of the clues. Physicians initiated about 30% — often by asking open-ended questions or initiating social questions about the patient's family or personal life.

3. Two thirds of the clues were emotional in nature, most often related to psychological and social concerns.
4. Physicians responded positively to patients emotions in about one case out of five.
5. Physicians frequently missed opportunities to adequately acknowledge patients' feelings. At times there was an extreme contrast between the patient's profound feelings and the physician's dismissive response.
6. In many visits, when the physician missed opportunities, the patient brought up the same issue a second or third time. Physicians almost always again missed the opportunity for support.
7. Visits with positive responses to clues did *not* take any longer than visits with missed opportunities.

## DISCUSSION

1. Outcomes of care are optimal when physicians address patients' emotional and personal concerns in addition to the biomedical problems.
2. Patients usually initiate clues in subtle ways, typically imbedded in the context of a discussion about a health problem. Physicians who are busy attending to the biomedical details and management may easily miss them.
3. "We do not believe it is essential, nor is it practical, for physicians to respond to emotional issues each time they are presented. In some cases, physicians may choose not to pursue a line of questioning, and it may have no consequences for the interview. In other cases, . . . a patient brings up the same emotional topic a second time during the encounter when the physician failed to address it on the first occasion. This allows physicians a second chance to discuss an emotional topic of importance to the patient."
4. "We do not find evidence that responding to clues lengthens visits."

## CONCLUSION

Patients often offer clues that present opportunities for their physicians to express empathy and understand patient's lives. Physicians often by-pass these clues, missing potential opportunities to strengthen trust and the patient-physician relationship.

Physicians can learn to modify their communication style.

JAMA August 23/30. 2000; 284: 1021-27 Original investigation, first author Wendy Levinson, University of Chicago, IL [www.jama.com](http://www.jama.com)

Comment:

Learning the art of listening to unspoken as well as spoken clues is a life-long quest. Empathic listening is an essential quality of good primary care. RTJ

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## **8-2 RATE OF HEART FAILURE AND 1-YEAR SURVIVAL FOR OLDER PEOPLE RECEIVING LOW-DOSE BETA-BLOCKER THERAPY AFTER MYOCARDIAL INFARCTION**

Treatment with beta-blockers (**BBs**) lowers mortality among individuals at high risk after myocardial infarction (**MI**), including elderly people. BBs also improve survival among patients with heart failure. Despite the proven benefits, not all eligible elderly people receive BBs after MI.

In clinical practice, of those who do receive BBs, treatment is commonly prescribed at doses lower than reported by randomized trials. This is perhaps because of fear of precipitating heart failure (**HF**). No trial investigated the minimum effective dose.

This study examined the relation between use of BBs, the dose used, and hospital admissions for HF in a cohort of older patients.

Conclusion: Low-dose therapy was associated with a lower rate of hospital admission for HF than high dose. One-year survival was similar.

### **STUDY**

1. Collected data on a cohort of over 13 000 patients aged over 65 who were discharged from the hospital after a MI. Some received no BB; some low-dose BBs; some standard doses; some high-dose. (*See table 1 p 640 for the variety of BBs used and dose range. For example for atenolol low dose was < 50 mg; standard dose 50 to 100 mg; high-dose > 100 mg.*)
2. Determined association of the dose with admission to hospital for HF and survival.

### **RESULTS**

1. Among over 8000 patients with no previous history of HF, dispensing of a BB was associated with a 43% reduction in subsequent admission for HF compared with patients not given BBs.
2. Among over 13 000 patients in the cohort 17% died by year one. Compared with those not dispensed BB therapy, the adjusted risk ratio for mortality was lower for all 3 doses: low dose — 0.40; standard dose — 0.36; high dose — 0.43.
3. There was a dose-related association between BB therapy and subsequent admission for HF.

Compared with the group receiving low-dose, those receiving high-dose were 53% more likely to be admitted for HF. Among over 2500 patients considered the most healthy, those prescribed high-dose therapy were more than twice as likely to be admitted for HF as those prescribed low-dose.

## DISCUSSION

1. Low-dose BB was associated with a 50% lower risk of hospital admission in the year following MI compared with high dose.
2. These results bridge new research evidence promoting the benefit of BB therapy for the management of HF. There is a long-standing belief that BB therapy may precipitate HF. This is more likely with high-dose therapy
3. "Consistent with previous trials, we found an association between use of beta-blockers and a lower rate of admissions for heart failure." Previous trials used titrated doses of BBs aiming at high-dose therapy. This study addressed the more subtle, but critical issue of the optimum dose. Higher doses were associated with higher risk of admission for HF, supporting the need to initiate BB at a low dose and to increase the dose gradually as tolerated.
4. Patients receiving low doses of BB (who are probably unable to tolerate higher doses) should continue their therapy. The potential survival benefit of low-dose BBs may encourage physicians to use these drugs in frail elderly people for whom BBs might not be prescribed. The group receiving low-dose BB included those who were older and most frail. This group may receive the most benefit from low-dose therapy.

## CONCLUSION

Compared with high-dose beta-blocker therapy, low-dose treatment was associated with a lower rate of hospital admission for heart failure and had a similar 1-year survival benefit.

Lancet August 11, 2000; 356: 639-44 Original investigation, first author Paula A Rochon, University of Toronto, Canada. [www.thelancet.com](http://www.thelancet.com)

### Comment

This reinforces the oft repeated dictum regarding BB therapy — "Start low and go slow".

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## 8-3 ALENDRONATE FOR THE TREATMENT OF OSTEOPOROSIS IN MEN.

Although osteoporosis is less common in men than in women, approximately 25% of all hip fractures occur in men, and many men have vertebral deformities. The number of hip fractures in men as well as in women is rising.

The causes of osteoporosis in men include an excess of glucocorticoids, hypogonadism, and a variety of other systemic conditions, medications, and lifestyle factors. Often there is no obvious cause. Primary osteoporosis (age-related and idiopathic) accounts for about 60% of all cases in men. Glucocorticoid-induced osteoporosis accounts for about 20%.

At present in the US, there are currently no approved therapies for men with osteoporosis. In men with hypogonadism, testosterone has limited efficacy.

This study asked -- does the bisphosphonate alendronate (*Fosamax*) prevent osteoporosis, or reverse bone loss in men with osteoporosis. (Alendronate inhibits osteoclast-mediated bone resorption.)

Conclusion: In men with osteoporosis, alendronate significantly increased bone mineral density and helped prevent vertebral fractures and decreases in height.

## STUDY

1. Two-year double blind trial entered 241 men (mean age = 63; range 31 to 87).
2. All had osteoporosis. (Ie, bone mineral density (**BMD**) at the femoral neck at least 2 standard deviations below the mean value of normal young men, and a BMD of the lumbar spine at least 1 SD below that of normal young men, or a BMD at the femoral neck at least 1 SD below normal and at least one vertebral deformity.
3. One third of subjects had low serum testosterone concentrations.
4. All received calcium and vitamin D supplements.
5. Randomized to: 1) alendronate 10 mg daily, or 2) placebo.
6. Follow-up = 2 years.

## RESULTS

1. Alendronate group had a mean increase in BMD of 7% at the lumbar spine, 2.5% at the femoral neck, and 2% total body.
2. Placebo group had an increase of 1.8 % in BMD at the lumbar spine, but no change elsewhere.  
(*Was the increase due to intake of calcium and vitamin D called for in the protocol? RTJ*)
3. Incidence of vertebral fractures was lower in the alendronate group 0.8% vs 7%
4. Men in the alendronate group lost less in height than the placebo group (0.6 mm vs 2.4 mm).
5. Alendronate was generally well tolerated. There were no significant differences in the incidence of



serious adverse events, withdrawals from therapy, or laboratory abnormalities between groups. Specifically, there were no differences in frequency of adverse GI events despite the fact that over 1/3 of men in both groups were taking NSAIDs.<sup>1</sup>

## DISCUSSION

1. In men, ten mg alendronate daily, given over 2 years, was associated with increase BMD of the spine, hip, and total body. Alendronate reduced incidence of vertebral fractures, and prevented decreases in height.
2. Effects were independent of baseline testosterone concentrations.
3. Effects on bone turnover, and changes in biochemical markers were consistent with those previously reported for post-menopausal women. The benefits and magnitude of improvement with alendronate therapy in men with osteoporosis were similar to those in postmenopausal women.

## CONCLUSION

In men with osteoporosis, alendronate significantly increased BMD and helped prevent vertebral fractures and decreases in height.

NEJM August 31, 2000; 343: 604-10 Original investigation, first author Eric Orwoll, Oregon Health Sciences University , Portland. [www.nejm.com](http://www.nejm.com)

Comment:

**1** Although not specifically described, those taking alendronate must have been instructed in proper use -- ie, empty stomach, followed by a full glass of water, and waiting 30 minutes before breakfast.

Adverse events would probably be higher in the real world than in the clinical trial world.

This presents a new challenge to primary care. Should anti-osteoporosis therapy be used in older men? How and when? Certainly all should receive adequate amounts of calcium and vitamin D. All should exercise as appropriate.

Obviously those taking corticosteroids and those with hypogonadism should receive preventive treatment. What about the great majority?

Visits to retirement homes will remind us of the frequency of bent-over, older men. This can be disabling. If preventable, it should be prevented. I would advise older men to have their height measured periodically. When the height begins to slip, I would consider a bisphosphonate. RTJ

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## 8-4 ASSOCIATION OF GLYCEMIA WITH MACROVASCULAR AND MICROVASCULAR COMPLICATIONS OF TYPE 2 DIABETES (UKPDS 35)

The UK Prospective Diabetes Trial compared a policy of intensive control of blood glucose vs conventional treatment in type 2 diabetes. Over 10 years, a HbA1c level of 7.0% was achieved in the treatment group vs 7.9% in the control. There was a considerable reduction in the risk of *micro*-vascular complications in the treatment group. But reduction in risk of myocardial infarction (a *macro*-vascular complication) was of borderline significance.

This study evaluated the risk between exposure to glycemia over time and development of *macro*-vascular as well as *micro*-vascular complications in patients with type 2 diabetes.

Conclusion: The risks of macro-vascular as well as micro-vascular complications were strongly associated with glycemia.

### STUDY

1. Prospective, observational study analyzed outcomes in over 3600 patients (mean age 53) with type 2 diabetes.
2. After a 3-month run-in period of dietary treatment, all had fasting blood glucose concentrations between 110 mg/dL and 270 mg/dL (6.1 to 15 mmol/L). None had symptoms of hyperglycemia.
3. Randomized to: 1) intensive policy of control with sulfonylureas or insulin, or 2) conventional control, primarily with diet. Aim of the treatment group was to obtain a fasting blood sugar < 110 mg/dL.
4. Baseline HbA1c was 7.1% in both groups. Control was followed periodically with HbA1c measurements.
5. Endpoints included:
  - A. Complicating *macro*-vascular events: myocardial infarction, stroke, lower extremity amputation, heart failure. Also death related to myocardial infarction; sudden death; stroke; or fatal peripheral vascular disease, renal disease.
  - B. Complicating *micro*-vascular events: retinopathy, vitreous hemorrhage, renal failure
6. Follow-up = 10 years.

### RESULTS

1. The risk of *macro*-vascular complications (as well as *micro*-vascular) was strongly associated with HbA1c concentrations after adjustments for age, sex, ethnic group, lipid concentrations, BP, smoking, albuminuria, and duration of diabetes. Incidence of complications increased with each higher category of updated mean HbA1c.

2. There was a three-fold increase in complication rate of those with HbA1c over 10% compared with those with HbA1c under 6%.
3. Even at near normal HbA1c levels, the risk of myocardial infarction (**MI**) was up to 3 times that of microvascular endpoints. The incidence of MI rose steadily as HbA1c rose from < 6% to 10%.
4. Mortality related to diabetes as well as all-cause mortality was strongly associated with glycemia.
5. Each 1% reduction in mean HbA1c was associated with reductions in risk of 21% for any endpoint related to diabetes, 21% for deaths related to diabetes, 14% for MI. And 37% for *micro*-vascular complications. Associations with glycemia were less steep for stroke and heart failure which are mainly related to BP.
6. There was no threshold HbA1c related to risk of any endpoint.

## DISCUSSION

1. There were highly significant associations between development of complications and the wide range of exposure to glycemia that occurs in type 2 diabetes. The risk remained after multiple adjustments for other known risk factors.
2. "Results suggest that ...the effect of hyperglycemia itself may account for at least part of the excess cardiovascular risk observed in diabetic compared with non-diabetic people beyond that explained by the conventional risk factors"
3. Hyperglycemia also has a crucial role in etiology of small vessel disease.
4. " Now that the UKPDS has shown that improved glucose control reduces the risk of complications and that the treatments are safe in clinical practice, a larger reduction of HbA1c might be achieved by earlier use of combination treatments or by the use of newer treatments which could further reduce the risk of myocardial infarction."
5. The nearer the HbA1c is to normal, the better. (However, it may be difficult to obtain and maintain near normal concentrations especially in those with high initial levels.)

## CONCLUSION

Cardiovascular and cerebrovascular disease account for more than 50% of all mortality in diabetic populations. The data suggest that any improvement in glycemetic control across the diabetic range is likely to reduce the risk of cardiovascular complications. Even a modest reduction in glycemia has the potential to prevent deaths from *macro*-vascular complications related to diabetes.

Glycemia is a risk factor for *macro*-vascular complications as well as *micro*-vascular complications.

BMJ August 12, 2000; 321: 405-12 Original investigation from the UKPDS, first author Irene M Stratton, Radcliffe Infirmary, Oxford UK. [www.bmj.com/cgi/content/full/321/7258/405](http://www.bmj.com/cgi/content/full/321/7258/405)

Comment:

The association between hyperglycemia and *micro*-vascular complications (retinal, renal, peripheral nerve) is well established. This is the first study I have encountered which strongly suggests that hyperglycemia is an independent risk factor for *macro*-vascular disease, especially MI. RTJ

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### **8-5 ASSOCIATION OF SYSTOLIC BLOOD PRESSURE WITH MACROVASCULAR AND MICROVASCULAR COMPLICATIONS OF TYPE 2 DIABETES. (UKPDS 36)**

This study is similar to the preceding, except that systolic BP, not the HbA1c level, was related to risk.

The incidence of clinical complications was significantly associated with *systolic* BP. Each 10 mm Hg decrease in updated mean systolic BP was associated with reductions in risk of 12% for any complication related to diabetes; 15% for deaths related to diabetes; and 11% for MI, and 13% for *micro*-vascular complications. The association persisted after adjustment for other risk factors — age, ethnic group, glycemia, lipid concentrations, smoking and albuminuria.

No threshold for risk related to systolic BP was observed.

Any reduction in BP is likely to reduce the risk of complications, with the lowest risk being in those with systolic BP less than 120.

Treatment with beta-blockers and ACE inhibitors may provide risk reductions above and beyond that associated with lowering BP.

BMJ August 12, 2000; 321: 412-19 Original investigation by the UK Prospective Diabetes Study Group, first author Amanda I Adler, Radcliffe Infirmary, Oxford, UK  
[www.bmj.com/cgi/content/full/321/7258/412](http://www.bmj.com/cgi/content/full/321/7258/412)

Comment:

This is the converse of the preceding investigation. The risk of *macro*-vascular complications related to systolic BP is well established. This study provides evidence that *micro*-vascular complications (renal retinal, and peripheral nerve) may also be related to systolic BP. RTJ

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### **8-6 CONTROLLING GLUCOSE AND BLOOD PRESSURE IN TYPE 2 DIABETES.**

When should treatment be started? What is the target level? What is the best method of treatment? "Since there are no obvious cut-off points for BP or glucose or cholesterol concentrations that would guide clinical decisions, the justification must come from clinical and epidemiological research."

Data from randomized trials are considered necessary these days for defining treatment practice, but there are limits on the generalisability of their results. These results are important in proving causality between risk factors and outcomes and in showing the reversibility of the disease process by therapy. Observational data, on the other hand, are necessary to describe the target population included in the trials and thus inform doctors how the trial results may be best translated to the community.

Target levels for glycemia, BP and lipids are based largely on expert opinions, with only limited evidence from trials. Epidemiological data clearly show there are no natural thresholds under which the risk of micro-vascular and macro-vascular complications are fully prevented. The risk rises steadily with rising levels of risk factors. This applies to both glycemia and systolic BP. But reaching artificial target levels does not fully protect patients against late complications.

Using multiple pharmacological agents in the short term (as in trials) may produce excellent results. However, it is difficult to maintain reductions in glucose and BP over time.

We must ask whether treatment to lower raised glucose should be started much earlier. Perhaps impaired glucose tolerance should be an indication for treatment.

BMJ August 12, 2000; 321: 394-95 Editorial by Jaako Tuomilehto, National Public Health Institute, Helsinki, Finland. [www.bmj.com/cgi/content/full/321/7258/394](http://www.bmj.com/cgi/content/full/321/7258/394)

Comment:

The clinical message is clear and important. To avoid complications control the HbA1c as close to 6% as possible and the systolic BP as low as possible. RTJ

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## **8-7 PRAVASTATIN THERAPY AND THE RISK OF STROKE**

Is there an association between lipid levels and stroke? A recent meta-analysis found no clear association. Some studies which classified stroke according to cause reported a positive association between increased cholesterol levels and ischemic stroke, and a negative association with hemorrhagic stroke.

This study assessed effects of the cholesterol-lowering statin drug pravastatin (*Pravachol*) on stroke from any cause in patients who had experienced a myocardial infarction or unstable angina. (Ie, a secondary prevention study.)

Conclusion: Pravastatin had a moderate effect in reducing risk of non-hemorrhagic stroke.

## STUDY

1. Double-blind, placebo-controlled trial compared effects of pravastatin with placebo on mortality due to coronary disease among over 9000 patients (mean age = 62). All had a history of myocardial infarction or unstable angina.
2. In this subset of the study the goal was to compare effect of pravastatin vs placebo on stroke from any cause and non-hemorrhagic stroke. (A secondary prevention study.)
3. Patients were taking a variety of cardiovascular drugs. These were continued.
4. Baseline median total cholesterol = 218; HDL-c = 36; LDL-c = 150; triglycerides = 140; total:HDL ratio = 6
4. Randomized to: 1) pravastatin 40 mg daily, or 2) placebo.
5. Follow-up = up to 6 years.

## RESULTS

1. 419 strokes occurred in 373 patients over the 6-year follow-up: 319 ischemic; 31 hemorrhagic; 79 unknown type.

2. Outcome	Placebo	Pravastatin	NNT
Total stroke	4.5%	3.7%	125
Non-hemorrhagic stroke	4.4%	3.4%	100
Hemorrhagic stroke	0.2%	0.4%	500 (to harm)

3. Pravastatin was associated with reduction in risk of cardio-embolic stroke, large-artery stroke, small artery stroke, and stroke of unknown origin.

4. Pravastatin had no benefit reducing hemorrhagic stroke.

5. Number (%) of patients with stroke according to baseline total cholesterol:

Baseline LDL cholesterol	Placebo	Pravastatin	NNT (benefit- 6 years)
< 135	5.1%	3.7%	71
135-173	4.6%	3.9%	142
> 173	3.6%	3.6%	-

## DISCUSSION

1. Lipid-lowering therapy with pravastatin reduced the risk of stroke in patients with known coronary disease (secondary prevention).
2. Benefits were achieved without adverse effects and without increasing the risk of hemorrhagic stroke.

3. Benefits of pravastatin were evident in the large subset of patients taking aspirin.
4. Of interest, total cholesterol and LDL-c levels at baseline revealed no evidence of differences in treatment effect. Benefit was more evident in those with a low HDL-cholesterol level.
5. "The benefits of pravastatin may be due to a number of mechanisms other than a lowering of lipid levels. Statins have other effects and may reduce the incidence of clinical events by influencing endothelial function, the inflammatory response, plaque stability, or thrombus formation."

## CONCLUSION

Lipid-lowering therapy with pravastatin was associated with a reduction in the rate of stroke as well as the rate of coronary disease in patients with established coronary disease. (Secondary prevention.)

NEJM August 3, 2000; 343: 317-26 Original investigation by the Long-Term Intervention with Pravastatin in Ischemic Disease" study, first author Harvey D White, University of Auckland, New Zealand. [www.nejm.com](http://www.nejm.com)

Comment:

There was no difference in benefits in those with initially more favorable lipid profiles vs those with less favorable (except the group with initially low HDL- levels). This surprised me. I expected that improving lipid profiles would be the main benefit of statin drugs.

The benefit of statins in secondary prevention of stroke over several years is minimal. Primary prevention would yield even less impressive results. The main reason to use statins is to stabilize coronary atherosclerosis. Benefits in other vascular beds are an extra-added attraction. RTJ

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## **8-8 STRONG AND SIGNIFICANT RELATIONSHIPS BETWEEN AGGREGATION OF MAJOR CORONARY RISK FACTORS AND THE ACCELERATION OF CAROTID ATHEROSCLEROSIS IN THE GENERAL POPULATION OF A JAPANESE CITY.**

Arterial intimal-medial thickness (IMT) measured by ultrasound is a non-invasive method to gauge progression and regression of atherosclerosis. IMT of the carotid arteries is a good indicator of the presence and extent of coronary artery disease.

This study asks: What is the relationship between an aggregation of coronary risk factors and carotid atherosclerosis?

Conclusion: Aggregation of established coronary risk factors strongly influenced carotid atherosclerosis.

STUDY

1. The study was based on a random sample of residents (age 30 to 80; n = 4000) in a large urban area of Japan. The population is strongly influenced by Westernization.
2. High resolution ultrasound of the carotid arteries detected: IMT, plaque number, plaque score, and percentage of stenosis.
3. Patients were classified according to the number of major coronary risk factors:
  - 1) hypertension (diastolic > 90; and /or systolic > 140), 2) smoking, and 3) hypercholesterolemia (total serum cholesterol > 220).

## RESULTS

1. The mean IMT value was higher in subjects with risk factors than in those without any risk factors:

	Men	Women
One risk factor	3.2% higher	2.9% higher
Two risk factors	6.3%	6.2%
Three risk factors	15.8%	15.4%

2. Mean plaque number and mean plaque score (total of the maximum thickness of all plaques in the same area) increased as the number of risk factors increased.
3. The percentage of subjects with stenosis > 50% increase stepwise with the number of risk factors especially in men. Women progressed more slowly.
4. Carotid abnormalities also increased with age even in those without risk factors.

## DISCUSSION

1. There were strong relationships between the aggregation of major coronary risk factors and differences in carotid atherosclerosis in a large general population of Japanese subjects.
2. The investigators suggest that carotid atherosclerosis of high risk persons progresses roughly 20 years ahead of those with no major risk factors. Progression in men seems to be about 10 years ahead of women.
3. The IMT of the carotid arteries is a reliable and powerful predictor of incident coronary events.
4. There is also a strong relationship between the integration of major risk factors and incidence of coronary events.
5. "Our data suggest that it is possible to infer non-invasively and correctly the extent of coronary atherosclerosis on the basis of carotid atherosclerosis." One recent study reported that, for each 0.03 mm increase in carotid IMT, the relative risk of myocardial infarction and coronary death = 2.2.
6. Ultrasonographic monitoring of early-phase carotid atherosclerosis may lead to the prediction



of coronary events.

## CONCLUSION

There was a strong relationship between the aggregation of 3 major risk factors (hypertension, high cholesterol, and smoking) and acceleration of progression of carotid atherosclerosis.

Archives Int Med August 14/28, 2000; 160: 2297-2303 Original investigation, first author Toshifumi Mannami, National Cardiovascular Center, Suita, Japan

Comment:

By concentrating on coronary disease, we often forget that atherosclerosis is a disease of all major arteries (aorta, renal, carotid, peripheral) and that risk factors are the same for all. Avoidance of risk factors reduces risk of all. We should be as protective of our brains and kidneys as we are of our myocardium. RTJ

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## 8-9 EFFECTS OF ESTROGEN REPLACEMENT ON THE PROGRESSION OF CORONARY-ARTERY ATHEROSCLEROSIS

Abundant observational data show that women receiving postmenopausal hormone replacement therapy (**HRT**) have fewer cardiovascular events than those who do not take HRT. HRT has favorable effects on cardiovascular risk factors.

However, the recent Heart and Estrogen/Progestin Replacement study<sup>1</sup> found no overall benefit of 4 years treatment with conjugated estrogen plus medroxyprogesterone on risk of non-fatal myocardial infarction and death from coronary heart disease in women with established coronary atherosclerosis. (Secondary prevention.) The subjects experienced an early *increase* in risk and a late *decline* in risk.

The present trial aimed to better understand the effect of estrogen of HRT on the progression of coronary atherosclerosis in women with established disease. (Secondary prevention)

Conclusion: HRT did *not* slow progression of coronary atherosclerosis in women with established disease.

## STUDY

1. Randomized, double-blind, placebo-controlled trial entered over 300 postmenopausal women (mean age 66). All had verified coronary disease.
2. Randomized to: 1) conjugated equine estrogen (*Premarin*) 0.625 mg daily, 2) conjugated equine estrogen 0.625 mg + medroxyprogesterone 2.5 mg daily, or 3) placebo.

3. Analyzed baseline and follow-up coronary angiograms.
4. Follow-up = 3 years.

## RESULTS

1. Both active treatments produced significant reductions in LDL-cholesterol and increases in HDL-cholesterol.
2. Neither treatment altered the progression of coronary atherosclerosis. At end-point, mean minimal coronary artery diameters were almost identical in all 3 groups, with no significant difference between them. Coronary artery diameter decreased in all groups. The degree of stenosis increased.
3. One or more new lesions developed in 30% of those taking estrogen, 20% of those taking combined therapy, and 33% of those taking placebo. (No significant difference)
4. Rates of clinical cardiovascular events (deaths from coronary disease, non-fatal MI, rates of revascularization, unstable angina and stroke) were similar among groups.

## DISCUSSION

1. Estrogen replacement for 3 years did *not* slow the progression of coronary atherosclerosis. Unopposed estrogen was no more effective than estrogen + progestin in slowing disease progression.
2. However, the progression of anatomically defined disease measures only one of several processes (eg, plaque stability, ulceration and thrombosis) that combine to produce acute ischemia.
3. How can the lack of treatment effect be explained, given the established effects of estrogen on lipids, endothelial function, and other factors in pathogenesis and progression of atherosclerosis? One possibility is that estrogen has proinflammatory effects.
4. Side effects such as vaginal bleeding, especially in the estrogen-alone group produced differential rates of compliance.
5. The trial did not allow drawing any definite conclusions about effects of treatment on clinical events.

## CONCLUSION

Three years of treatment with estrogen and estrogen-progestin did not slow progression of coronary atherosclerosis in postmenopausal women who had established disease at baseline.

"These results suggest that such women should not use estrogen replacement with an expectation of cardiovascular benefit."

"Estrogen therapy may still be effective for the *primary* prevention of coronary heart disease, but this has not yet been verified."

NEJM August 24, 2000; 343: 522-29 Original investigation, first author David M Herrington, Wake Forrester University School of Medicine, Winston-Salem, NC.

1 JAMA 1998; 280: 605-13 [www.jama.com](http://www.jama.com)

Comment:

The hypothesis that HRT reduces risk of postmenopausal cardiovascular events is certainly not yet abandoned. The biological plausibility for benefit is strong — the marked increase in incidence of CHD in the postmenopause when estrogen levels fall; the benefit on lipid profiles and endothelium

Data at present indicate that, in women with established CHD, estrogen may be harmful, especially in the short term after beginning therapy. But as yet, no study has reported harm over the long-term.

I would not prescribe HRT in women with established disease. But benefit in women without coronary atherosclerosis who begin therapy at menopause is still a reasonable possibility.

As the investigators imply, the anatomical degree of coronary atherosclerosis is not a good predictor of coronary events. Most thrombotic episodes causing myocardial infarction or unstable angina occur in lesions with less than 50% obstruction — due to an unstable plaque. Benefit or harm of HRT is likely due to effects other than on the degree of atherosclerosis.

See the following. RTJ

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## **8-10 TRENDS IN THE INCIDENCE OF CORONARY HEART DISEASE AND CHANGES IN DIET AND LIFESTYLE IN WOMEN**

This study examined trends in incidence of CHD from 1980 to 1994 among women. It reports detailed data on dietary and other lifestyle factors related to the incidence of CHD and the degree to which diet and lifestyle might account for these trends.

Conclusion: Reduction in smoking, improvement in diet, and increase in postmenopausal hormone use accounted for much of the decline in incidence of CHD over 15 years.

### **STUDY**

1. The Nurses' Health Study followed over 85 000 women age 34 to 59 at baseline. None had previously diagnosed cardiovascular disease or cancer.
2. Assessed lifestyle variables at baseline and reexamined them periodically.
3. Determined incidence of CHD over time.

### **RESULTS**

1. After adjustment for age, the incidence of CHD declined by 31% from 1980-82 to 1992-94. %.  
The decline in CHD was evident in all age groups.
2. The prevalence of current smoking declined from 27% to 16%

3. The proportion of postmenopausal women using hormone replacement therapy (**HRT**) increased from 16% to 44%.
4. Overweight (BMI over 25) increased from 37% to 51%.
5. Diet improved substantially. Average intake of trans fat decreased by 31%; ratio of polyunsaturated to saturated fat increased by 69%; intake of cereal fiber increased by 90%; margarine n-3 fatty acids increased by 180%; folate by 12%.
6. The average intake of beef, pork, lamb declined from 1.1 servings daily to 0.7 servings; high fat dairy products declined; low-fat dairy products increased; poultry and fish increased.
7. Only one food factor showed an adverse trend — glycemic load increased by 22%.
8. No appreciable change in levels of physical activity.
9. Statistically, changes in these variables, taken simultaneously, explained a 21% decline in incidence of CHD (representing 68% of the overall decline). Individually, smoking explained a 13% decline; improvement in diet — 16%; and increased use of HRT — 9%.
10. The increase in BMI explained an 8% increase in incidence of CHD.

## DISCUSSION

1. Cessation of smoking, improvement in diet and use of HRT statistically explained much of the decline in CHD.
2. Except for an increase in glycemic load and an increase in energy intake, the diet improved substantially.
3. In contrast, increased incidence of obesity adversely affected the trend. "The incidence of coronary heart disease would probably have declined even more if the body-mass index had not increased."
4. The decline in incidence of CHD was primarily in non-fatal myocardial infarction.
5. Other factors such as levels of BP and serum lipids also may have contributed to changes in incidence of CHD.

## CONCLUSION

There was a substantial decline in incidence of CHD from 1980 to 1995 among women in the Nurses' health Study. Reductions in smoking, improvement in diet, and increase in HRT accounted for much of the improvement.

Increase in the incidence of obesity appears to have prevented a further improvement.

These factors are important in primary prevention of CHD.

NEJM August 24, 2000; 343: 530-37 Original investigation, first author Frank B Hu, Harvard School of Public Health, Boston Mass. [www.nejm.com](http://www.nejm.com)

Comment:

The epidemiological evidence of benefit from HRT persists. A possible confounder —the "healthy user effect" also persists. The authors state that the data may not be extrapolated to the general population because all subjects were nurses.

I believe at present clinicians will continue to advise HRT for most women at menopause because of its obvious benefits on symptoms and osteoporosis — while realizing the downside of increase in breast cancer and thromboembolic disease. I choose to interpret the evidence as beneficial in the primary prevention of CHD in women without established CHD, beginning at the time of menopause (not years later). This article adds some data to support this approach. RTJ

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## **8-11 COGNITIVE DECLINE IN WOMEN IN RELATION TO NON-PROTEIN BOUND OESTRADIOL CONCENTRATIONS**

Studies concerning a relationship between estrogen therapy and cognitive function have yielded conflicting results. Indeed, the authors of this study reported in a previous study that serum concentrations of total estradiol and estrone were *not* consistently associated with cognitive function or risk of decline in cognitive function in older women.

However, total hormone concentrations may not be the best measure of biological effects. Non-protein-bound (free) and loosely bound (bioavailable) forms cross the blood-brain barrier and may be better correlated with cognitive function.

This study asked: Are serum concentrations of non-protein-bound and bioavailable estradiol related to risk of cognitive impairment in older women?

Conclusion: Women with high concentrations were less likely to develop cognitive impairment.

### **STUDY**

1. Entered over 400 women over age 65 (mean age 72) who volunteered for the study. They completed a 3-hour interview in which most showed high cognitive function.
2. Measured cognitive performance with a modified mini mental status examination at baseline, and 6 years later.
3. Measured concentrations of non-protein-bound and bioavailable estradiol at baseline. Divided cohort into tertiles according to the concentrations; 32% of the high tertile were taking oral estrogens vs 5% in the lowest tertile.

4. Follow-up = 6 years.

## RESULTS

1. Cognitive impairment ( a decrease of 3 points or more in the MMSE score):

High tertile of serum concentrations 5%

Low tertile 16%

2. After multiple adjustments for possible confounders, the odds ratio of cognitive dysfunction in the highest tertile vs the lowest was 0.3.

## DISCUSSION

1. Unbound and loosely bound estrogen serum concentrations were associated with a lower risk of cognitive dysfunction in older postmenopausal women. Possibly this is the form of estrogen related to cognitive function since in these forms estradiol crosses the blood-brain barrier.
2. The investigators also reported an association between high bone mineral density (a marker of life-long estrogen exposure) and better cognitive function.
3. "A low dose of oestrogen, to increase concentrations slightly, but not into the range of premenopausal concentrations, could be sufficient to prevent outcomes such as osteoporosis and cognitive impairment, but not enough to increase risk of breast cancer or deep-vein thrombosis."

## CONCLUSION

Older women with high concentrations of non-protein-bound and bioavailable estradiol were less likely to develop cognitive dysfunction than women with low concentrations.

Lancet August 26, 2000; 356: 708-12 Original Investigation, first author Kristine Yaffe, University of California, San Francisco [www.thelancet.com](http://www.thelancet.com)

An editorial in this issue (pp 694-5) comments;

"These findings are especially exciting because they suggest that women who have low concentrations of these hormones are likely to show the most benefit from the cognitive-enhancing effects of HRT, and that this benefit may be obtained with a low dose of estrogen. Because of the increased risk of breast cancer and thromboembolic events associated with HRT, the prospect of being able to use lower doses of oestrogen and to target women who will benefit most, is tremendously appealing."

However, as usual, "Replication with a more representative sample is required".

Comment:

What is the clinical message? I have not read that estrogen concentrations or estrogen therapy are associated with a decline in cognitive function.

I believe it is reasonable to suggest to our post-menopausal women patients that there is tentative evidence that estrogen replacement is associated with cognitive benefit. This in addition to the other benefits may lead more women to accept HRT. The suggestion that lower doses (eg, 0.3 mg of conjugated estrogen vs the usual 0.625 mg) may be associated with as much benefit is an important clinical application.

Are we making any progress in prevention of the cognitive decline with increasing age? This study and the recent tentative evidence that statin drugs may delay onset of cognitive decline are encouraging.

RTJ

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## **8-12 THE TIMI RISK SCORE FOR UNSTABLE ANGINA/NON-ST ELEVATION MI A Method for Prognostication and Therapeutic Decision Making**

Patients presenting with an acute coronary syndrome without ST-segment elevation are diagnosed as having unstable angina/non-ST elevation myocardial infarction (**UA/NSTEMI**). The condition is heterogeneous. Patients have a wide risk of death and cardiac ischemic events.

The objective of this study was to develop a simple risk score that has broad application, is easily calculated at patient presentation, does not require a computer, and identifies patient with different responses to treatment of UA/NSTEMI.

### **STUDY**

1. Two international randomized, double-blind trials (see citations) entered almost 7000 patients with UA/NSTEMI.
2. All patients presented within 24 hours of an episode of UA/NSTEMI at rest.
3. Additional enrollment criteria included at least 1 of the following: ST depression, documented history of coronary artery disease (**CAD**), and elevated serum cardiac markers.
4. All patients received aspirin and then were randomized to: 1) subcutaneous enoxiparin (*Lovenox*), or 2) intravenous unfractionated heparin.
5. End point was a composite of all-cause mortality, new or recurrent MI, or severe recurrent ischemia prompting urgent revascularization.
6. Follow-up = 14 days after randomization.
7. Constructed a score based on 7 variables that had previously been found to be statistically

significant predictors of events. (Score 1 if the variable was present and 0 if not present.) The sum of the number of factors categorized patients into risk strata.

## RESULTS

1. Seven risk score predictor variables were:

Age over 65

At least 3 risk factors for CAD

Prior coronary stenosis over 50%

ST deviation on presentation

At least 2 anginal events in the prior 24 hours

Use of aspirin in the past 7 days

Elevated serum cardiac markers.

2. Event rates — (combined all cause mortality, myocardial infarction and severe ischemia requiring urgent revascularization) increased significantly as the TIMI score increased:

0/1	2	3	4	5	6/7
5%	8%	13%	20%	26%	41%

3. As risk score rose from 0/1 to 6/7, all cause mortality rose from 1% to 7 %; MI from 2% to 16%; urgent vascularization from 1% to 21%; and all cause mortality or non-fatal MI from 3% to 19%

4. The slope of the increase in event rates was significantly lower in the enoxiparin groups..

## DISCUSSION

1. The simple arithmetic sum of the number of these variables can be calculated easily.

2. The risk score categorizes UA/NSTEMI into groups that span a wide range of risk for clinical events.

3. Treatment with the low-molecular weight heparin enoxiparin was superior to unfractionated heparin. The corresponding number needed to treat with enoxiparin (as compared with unfractionated heparin) to prevent 1 event decreased as the risk score increased. (Ie, enoxiparin was more beneficial.)

4. Risk assessment of patients with UA/NSTEMI is a continuous process that initially involves integration of data at presentation and later incorporates hospital-phase data such as the results of invasive and non-invasive testing, monitoring of episodes of recurrent ischemia, and response to initial therapy. The TIMI risk score presented here was designed for prognostication at the time of initial presentation.

## CONCLUSION



In patients with UA/NSTEMI the TIMI risk score is a simple prognostic scheme that categorizes a patient's risk of death and ischemic events. It provides a basis for therapeutic decision-making. The low-molecular-weight heparin enoxiparin was more beneficial than unfractionated heparin.

JAMA August 16, 2000; 284: 835-42 Original investigation, first author Elliott M Antman, Brigham and Woman's Hospital, Boston, Mass. [www.jama.com](http://www.jama.com)

Comment:

I abstracted this article in part because of the reported greater benefits of the low-molecular weight heparin given subcutaneously, compared with intravenous unfractionated heparin. This makes therapy much simpler. RTJ

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### **8-13 SMOKING, SMOKING CESSATION AND LUNG CANCER IN THE UK SINCE 1950**

This paper relates the UK national trends in smoking, smoking cessation, and lung cancer. It contrasts results from two large case-control studies conducted 40 years apart (1950s and 1990s).

The 1950s study was concerned with identifying the main causes of the rise in lung cancer and showed the predominant role of tobacco.

Because there has been a wide-spread cessation of smoking (indeed, above age 50 there are now twice as many former smokers as current smokers in the UK), the 1990s study was able to assess the long-term effects of giving up the habit at various ages.

Conclusion: People who stopped smoking, even well into middle-age avoided most of their subsequent risk of lung cancer.

#### **STUDY**

1. Determined UK national trends in smoking, smoking cessation, and lung cancer by contrasting results of case control studies conducted 40 years apart — in the 1950 and 1990s.
2. Because there had been a wide-spread cessation of smoking, the 1990s study was able to assess the long-term effects of giving up the habit at various ages. (Indeed, above the age of 50, there are twice as many former smokers as current smokers.)

#### **RESULTS**

1. Current smokers in 1990s:

Most of the participants who were still current cigarette smokers in 1990s would have been

smokers throughout adult life. The cumulative risk of lung cancer by age 75 in this group was 16% for men and 10% for women.

About 33% of men and 10% of women who were current smokers in 1990s had started smoking before the age of 15. This group had double the risk of lung cancer compared with those who started after age 20.

### 3. Quitters by 1990s:

Since a large number of men had stopped smoking well before 1990s, robust estimates could be obtained from the 1990s data on the effects of cessation on incidence of lung cancer.

Smoking status in 1990s	Risk ratio of lung cancer
Current smoker	1.00
< 10 years cessation	0.66
10-19	0.44
20-29	0.20
>30	0.10
Lifetime non-smoker	0.03

4. Among both men and women in 1990s, former smokers had only a fraction of the lung cancer rate of continuing smokers, and this fraction fell steeply with time since stopping.

5. By 1990, cessation had almost halved the number of lung cancers that would have been expected if the former smokers had continued. For men who stopped at ages 60, 50, 40, and 30, the cumulative risks of lung cancer by age 75 were 10%, 6%, 3% and 2%.

## DISCUSSION

1. In the 1990s study the effects of prolonged cessation among those who had smoked cigarettes for many years before, could be assessed.
2. If people who have been smokers for many years stop, even well into middle age, they avoid most of the subsequent risk of lung cancer.
3. Widespread cessation has already approximately halved the lung cancer mortality that would have been expected.
4. "Mortality from tobacco in the first half of the 21st century will be affected much more by the number of adult smokers who stop than by the number of adolescents who start."

## CONCLUSION

Smokers who stop even well into middle age avoid most of their subsequent risk of lung cancer. Stopping before middle age avoids more than 90% of the risk attributable to tobacco.

Mortality throughout the first half of the 21st century could be substantially reduced by current smokers giving up the habit.

Young persons who begin to smoke now will henceforth become statistics in the middle and second half of the century.

The good news — it's never too late to stop

BMJ August 5, 2000; 321: 323-29 Original investigation, first author Richard Peto, Radcliffe Infirmary, Oxford UK [www.bmj.com/cgi/content/full/321/7257/323](http://www.bmj.com/cgi/content/full/321/7257/323)

Comment:

The clinical message is clear and important — it is never too late to stop. Benefits regarding COPD will accrue in addition to the effect on cancer. RTJ

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#### **8-14 LONG-TERM SAFETY AND EFFICACY ON OMEPRAZOLE IN GASTRO-OESOPHAGEAL REFLUX DISEASE.**

Recent data suggest that open fundoplication and omeprazole are similarly effective in treatment of GERD provided that medical therapy can be increased in response to recurrent symptoms or erosions.

Proton-pump inhibitors (**PPIs**) are the mainstay of therapy for gastro-esophageal reflux disease. What about long-term safety?

This editorial cites a recent study<sup>1</sup> of over 200 patients with erosive esophagitis who received maintenance therapy for a mean of over 6 years.

In the study, the dose was titrated against symptoms. Requirements seemed to increase gradually with time, as did the proportion of patients requiring more than 40 mg daily.

Remission was maintained in all patients.

Inhibition of acid secretion induces hypergastrinemia. This raises the specter of gastric carcinoids, gastric carcinoma, and colonic carcinoma because of gastrin's trophic effects on stomach and colon. However, the gastrin concentrations during PPI therapy are much lower than those occurring in pernicious anemia and the Zollinger-Ellison syndrome.

In the study, adverse effects were reported and common, but their types and frequencies seemed unremarkable for the elderly population under study. None required the dose to be reduced.

Long-term therapy was safe and effective.

Lancet August 19, 2000; 356: 610-112 Editorial by David Armstrong, McMaster University Medical Centre, Hamilton, Ontario, Canada [www.thelancet.com](http://www.thelancet.com)

1 Gastroenterology 2000; 118: 661-69

Comment:

COST: My pharmacy quotes a cost of *Prilosec* of \$110 for thirty 20 mg tablets — \$1320 per year. Over \$2000 a year for 40 mg.

Patients should express preference — continue medical therapy indefinitely, or undergo surgery?

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### **8-15 PREDICTORS OF OUTCOME IN SEVERE, ASYMPTOMATIC AORTIC STENOSIS**

The poor outcome of patients with symptomatic aortic stenosis (**AS**) is well known. In view of the excellent results of aortic valve replacement, surgery is strongly recommend for these patients.

What about management for asymptomatic AS? Controversy remains. The occurrence of sudden death in asymptomatic patients and the potential risk of irreversible myocardial damage argues for early elective surgery. However, the wide variation in individual outcomes, the potential risk of complications related to the prosthetic valve, and the risk of surgery itself make decisions difficult. Identification of predictors of outcome could help in selecting patients who are likely to benefit from early surgery.

This study prospectively examined patients with severe asymptomatic AS to identify predictors of outcome.

Conclusion: Moderate to severe valve calcification, together with a rapid increase in aortic-jet velocity identifies a group with poor prognosis for which early surgery should be considered.

#### **STUDY**

1. Identified 128 consecutive patients (mean age = 60) with severe AS who were without symptoms. Patients with mild fatigue and mild dyspnea during maximal exercise were not excluded because of the non-specificity of these symptoms.
2. All had a stenotic native valve and a peak aortic ejection velocity of at least 4 m per second. (Mean aortic jet velocity = 5 m per second).
3. All had normal left ventricular function, except 2 with coronary disease.
4. Definitions: mild calcification — small isolated spots; moderate — multiple larger spots; and severe —  
extensive thickening and calcification of all cusps.
5. Followed prospectively for 4 years. End-points = death, or valve replacement necessitated by the development of symptoms.

## RESULTS

1. Death occurred in 6 patients. Five of 6 deaths were preceded by symptoms.
2. 59 patients had valve replacement necessitated by development of symptoms.
3. Event free survival: 67% at 1 year; 56% at 2 years; and 33% at 4 years.
4. Only the extent of aortic-valve calcification was an independent predictor of outcome:

Event-free survival	No or mild calcification: Moderate or severe calcification:	
	1 year	92%
2 years	84%	47%
4 years	74%	20%

5. The rate of progression of stenosis also provided useful prognostic information: Of the patients with moderate to severe calcification, whose aortic-jet velocity increased by 0.3 m per second or more within 1 year, 79% underwent surgery or died within 2 years.

## DISCUSSION

1. Many physicians are reluctant to refer patients with severe aortic stenosis for valve replacement as long as they are without symptoms. The great majority of patients with asymptomatic AS do *not* have impaired left ventricular function (in contrast with those with valvular regurgitation). Nevertheless, myocardial fibrosis and severe hypertrophy may occur if surgery is delayed and may preclude optimal surgical outcomes.
2. The outcome after valve replacement is excellent in patients with normal preoperative left ventricular function. Once symptoms appear, and urgent valve replacement is required, the operative mortality becomes higher.
3. The extent of valvular calcification was a strong independent predictor of outcome.
4. Aortic-jet velocity was higher in patients who had cardiac events, but the differences were small. The marked overlap precluded drawing any conclusions about outcome in an individual patient. Results suggest that assessment of the rate of progression of aortic-jet velocity by serial echocardiographic examination may yield important prognostic information.
5. "Although current practice guidelines do not recommend surgery for asymptomatic patients with severe aortic stenosis (citation # 17 p 617), their optimal treatment remains controversial, and some physicians decide to refer their patients for valve replacement despite the lack of data to support this strategy."

## CONCLUSION

In asymptomatic patients with AS, it appears relatively safe to delay surgery until symptoms develop, However, outcomes vary widely. The presence of moderate or severe calcification, together with a rapid increase in aortic-jet velocity, identifies patients with a very poor prognosis. These patients should be considered for early valve replacement rather than have surgery delayed until symptoms develop.

NEJM August 31, 2000; 343; 611-17 Original investigation, first author, Raphael Rosenhek, Vienna General Hospital, Austria. [www.nejm.com](http://www.nejm.com)

Comment:

Is "asymptomatic-severe aortic stenosis" an oxymoron?

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## **8-16 AORTIC STENOSIS — LISTEN TO THE PATIENT, LOOK AT THE VALVE**

Aortic stenosis may be due to rheumatic disease or to calcification of a congenitally bicuspid or normal valve. Calcific aortic valvular disease is by far the most common valve lesion in the US.

"Clinically significant obstruction of flow is present in about 1 to 2 percent of adults over age 65, and it is likely that most of these patients will ultimately have symptoms necessitating valve replacement."

Calcific valvular disease is not simply a degenerative condition associated with aging. It represents the end stage of an active disease process. In the early stages, the aortic side of the valve contains focal lesions characterized by thickening of the subendothelium and adjacent fibrosa (the central collagenous layer of the leaflet). Areas of microscopic calcification occur within regions of lipoprotein accumulation. This stage of the disease is evident on echocardiography as mild, irregular leaflet thickening without obstruction to outflow. It is termed aortic *sclerosis*. Prevalence of aortic sclerosis increases with age; it is present in about 25% of persons over age 65.

As the disease progresses, calcification and fibrosis lead to leaflet stiffness and a reduced systolic opening, and eventually to a reduction in the valve area and an increase in forward velocity. The simplest measure of the extent of stenosis is the forward velocity across the valve. Normally, this is about 1.0 m per second. It increases to 2.5 to 2.90 m per second in mild; to 3.0 to 4.0 m per second in moderate; and to over 4.0 in severe stenosis.

Unlike the situation in patients with aortic regurgitation, in whom volume overload leads to progressive dilation and left ventricular dysfunction, systolic function is typically preserved in patients with AS. Even if systolic function is depressed late in the course of the disease, systolic function improves after valve replacement, thanks to the resultant decrease in afterload. In AS, contrasted to aortic regurgitation, clinical outcome is most closely related to presence or absence of symptoms. But, once symptoms occur, clinical outcome is extremely poor. However, this dismal prognosis can be

reversed by valve replacement with acceptable levels of operative mortality and morbidity.

Postoperative survival is similar to that of age-matched normal adults.

"In contrast, adults with asymptomatic aortic stenosis may have an excellent clinical prognosis."

There is substantial variation in the degree of stenosis associated with the onset of symptoms. The presence of moderate to severe calcification and increasing aortic-jet velocity over time as reported in the preceding study are strong predictors of outcomes.

The editorialist agrees that the optimum time to perform valve replacement is as soon as symptoms develop. However, progressively severe stenosis may occur in asymptomatic patients. Symptoms could be expected within the next year. Patients might then consider surgery if they understand the risks and benefits.

We need to educate patients with AS about the expected course of the disease. Once symptoms appear, prompt surgery is indicated. The onset of symptoms may, however, be insidious, and patients may incorrectly attribute a decrease in exercise tolerance to "getting older" or "the flu", when, in fact, it is time for valve replacement.

Listen to the patient's symptoms, look at the valve by echo.

NEJM August 31, 2000; 343: 652-54 Editorial by Catherine M Otto, University of Washington School of Medicine, Seattle. [www.nejm.com](http://www.nejm.com)

Comment:

Sooner, or later, if you practice primary care medicine, you will encounter a patient with AS. What advice should you give? Certainly seek a consultation from a cardiologist to assess severity and progression. I believe the primary care physician has a better opportunity than the specialist to assess onset and progression of symptoms. And to make sure that the patient seeks periodic rechecks by echo.

It seems reasonable to me to seek earlier surgery (even if the patient denies symptom increase) when progression is rapid and the stenosis severe. Waiting for development of co-morbidity (coronary disease, worsening hypertension, diabetes, stroke, COPD) will greatly increase risks of surgery.

The study found that increasing age, presence of coronary disease, and diabetes increased risk, but were not considered independent predictors of outcome. However, on an empirical basis, most clinicians would believe their presence, as well as hypertension, lipid abnormalities, and co-morbid diseases would affect risks of delaying surgery, and of surgery itself.

Interestingly, occurrence of left ventricular hypertrophy and ECG changes related to hypertrophy and other cardiac abnormalities were not mentioned as risk factors. But, they occur with AS, and do increase risk.

If I had AS and it was progressing on objective study, I would opt for early surgery before symptoms appear — before the myocardium is damaged. RTJ

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## **8-17 EFFECT OF INTRAVENOUS OMEPRAZOLE ON RECURRENT BLEEDING AFTER ENDOSCOPIC TREATMENT OF BLEEDING PEPTIC ULCERS**

Bleeding recurs in about 20% of patients after endoscopic treatment of bleeding peptic ulcers (PU).

In vivo studies have shown that a high intragastric pH facilitates platelet aggregation and clot formation.

Although histamine H<sub>2</sub>-receptor blockers raise pH to some extent, evidence of their effectiveness in bleeding PUs is conflicting.

This study assessed effectiveness of the proton pump inhibitor omeprazole (*Prilosec*) which maintains intragastric pH at near neutral levels. Does omeprazole, given iv, reduce rate of recurrence of bleeding after endoscopic treatment of bleeding?

Conclusion: Omeprazole substantially reduced recurrence rate.

### **STUDY**

1. Enrolled 240 patients with actively bleeding PU. All were treated with epinephrine injection followed by thermocoagulation.
2. After hemostasis had been achieved, randomized to: 1) iv omeprazole 80 mg bolus followed by 8 mg/h for 72 hours, or, 2) placebo.
3. All patients were then given 20 mg omeprazole daily for 8 weeks. Endoscopy was used to confirm episodes of rebleeding.

### **RESULTS**

1. Bleeding recurred in 7% of omeprazole group vs 23% in placebo group.
2. Most episodes of bleeding occurred in the first 3 days. (Ie, during the omeprazole infusion period.)
3. Three in the omeprazole group and 9 in the placebo group underwent surgery.
4. Five in the omeprazole group died within 30 days vs 12 in the placebo group.

### **DISCUSSION**

1. In another study, 220 patients who did not undergo endoscopic treatment (they had a non-bleeding visible vessel or a clot) were significantly less likely to have further bleeding when given an oral dose of 40 mg omeprazole twice daily for 5 days.



## CONCLUSION

After endoscopic treatment of active bleeding from a peptic ulcer, high-dose omeprazole given iv substantially reduced risk of rebleeding.

NEJM August 3, 2000; 343: 310-16 Original investigation from the Chinese University of Hong Kong, China [www.nejm.com](http://www.nejm.com)

Comment:

The Hong Kong physicians have been very active in reporting studies on peptic ulcer. I suspect PU is more common in China. But it remains common in the US.

Bleeding PU is still a lethal disease. The use of proton pump inhibitors is a welcome advance in therapy.

An editorial in this issue (*pp* 358-59) comments that iv omeprazole is not available presently in the US. The oral form may be used, but is not as effective in rapidly raising the intragastric pH. RTJ

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## 8-18 DURATION OF SYMPTOMS AND PLASMA CYTOKINE LEVELS IN PATIENTS WITH THE COMMON COLD TREATED WITH ZINC ACETATE

Ten controlled trials of zinc lozenges in treatment of the common cold have been published — 5 reported benefit; 5 reported no benefit. Two trials examined viral shedding in volunteers who were inoculated with rhinovirus and were treated with zinc. Conclusion — no effect.

Some biological plausibility of zinc treatment is based on the observation that it prevents the formation of viral capsid proteins, inhibiting in vitro replication of several viruses, including rhinovirus.

This study assessed the duration of cold symptoms in zinc-treated vs placebo-treated patients.

Conclusion: Zinc lozenges were associated with a reduced duration and severity of cold symptoms.

## STUDY

1. Randomized, double-blind, placebo-controlled trial entered 50 ambulatory volunteers (mean age 37) within 24 hours of beginning symptoms of the common cold.
2. Randomized to: 1) one zinc acetate lozenge (12.8 mg) every 2 to 3 hours when awake, or 2) placebo lozenges. Treatment was continued as long as they had cold symptoms.
3. Both lozenges contained several flavorings. "The placebo and zinc lozenges were identical in weight, appearance, flavor, and texture."

4. Recorded symptom scores for sore throat, nasal discharge, nasal congestion, sneezing, cough, scratchy throat, hoarseness, muscle aches, fever, and headache for 12 days.
5. Determined plasma pro-inflammatory cytokine levels on day 1 and after recovery.

## RESULTS

1. Compared with the placebo group, the zinc group had:
  - Shorter mean overall duration of cold symptoms (4.5 vs 8.1 days)
  - Shorter duration of cough (3.1 days vs 6.3)
  - Shorter duration of nasal discharge (4.1 days vs 5.8)
2. The zinc patients had decreased total severity scores for all symptoms.
3. Differences in pro-inflammatory cytokine levels were not significant.
4. Of those taking zinc, 5% correctly guessed that they were receiving active therapy. Of the placebo patients 10% correctly guessed they were taking placebo. (The investigators considered this no greater than a guess by chance.)
5. No difference in side effects occurred except that constipation and dryness of the mouth were reported more often in the active treatment group.

## DISCUSSION

1. "We found that treatment with zinc acetate lozenges was associated with decrease in the average duration and severity of the common cold."
2. The study determined no antiviral effect. Viral cultures were not done.
3. With use of high dose zinc lozenges for 6 to 8 weeks, copper deficiency is likely to occur. Zinc therapy for the common cold should be limited. "We recommend that if a person does not show clear evidence of improvement after 3 days of zinc treatment, he or she should be investigated for other respiratory tract disorders or allergy."
4. Tremacamra, a soluble intercellular adhesion molecule drug that functions as a receptor blocker, was recently shown to be effective in treatment of experimental rhinovirus infections.

## CONCLUSION

Treatment with zinc lozenges was associated with reduction in the duration and severity of symptoms of the common cold.

The investigators comment on the source of funding. The George and Patsy Eby Research Foundation, Austin Texas, donated unrestricted research funds to Wayne State University for partial support of this study. The research foundation had no role in the collection, analysis, or interpretation of the data, or in the decision to publish the study. George Eby holds U.S. patent rights for zinc lozenges and donated funds earned from his patent rights to the research foundation. He supplied the zinc and placebo lozenges for this study, The authors have neither industry connections nor personal financial conflicts of interest related to the study.

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## **8-19 LESSONS LEARNED FROM ATTEMPTS TO ESTABLISH THE BLIND IN PLACEBO-CONTROLLED TRIALS OF ZINC FOR THE COMMON COLD**

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

"Anything tasting as bad as zinc and with as much aftertaste as zinc must be good medicine. "

In most randomized, placebo-controlled, double-blind trials, the methods section indicates that patients were randomly assigned to an active drug or an "identical placebo". The empirical basis for this statement is rarely mentioned. Ideally researchers demonstrate that patients could not differentiate between the placebo and the study drug. For most drug studies, clinical researchers obtain the placebo from drug companies and usually take on faith that it is "identical" and that the blind has been established.

In practice, to prove that blinding has been established, researchers have begun to ask patients to guess whether they are taking placebo or active drug.

The problem becomes daunting for drugs whose physical characteristics make blinding difficult — eg, drugs that are not bland or neutrally colored, that cannot be placed in a capsule, that leave an aftertaste, or that cannot be swallowed quickly.

The preceding study stated that the zinc lozenges and placebo were "identical in weight, appearance, flavor, and texture". However, the editorialist calculates from the data that more than 3 times as many participants who received zinc guessed that they were given zinc as those who were given placebo. The authors attributed this to chance. The editorialist suspects that the placebo and the zinc had detectable differences, and that the blind was not completely established.

Could imperfect blinding have biased the study? The editorialist believes the effect of zinc on the common cold is still questionable.

Asking patients to guess whether they are taking placebo or active drug should become a standard feature of all randomized, double-blind, placebo-controlled trials.

Annals Int Med August 15, 2000; 133: 302-03 Editorial by Norman A Desbiens, University of Tennessee College of Medicine, Chattanooga Unit. [www.annals.org](http://www.annals.org)

Comment:

The editorialist remains unconvinced. I believe the problem is that there are no plausible data establishing a biological action of zinc. RTJ

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### **8-20 RAPID DIAGNOSIS OF FALCIPARUM MALARIA BY USING THE PARASIGHT F TEST IN TRAVELERS RETURNING TO THE UNITED KINGDOM**

This simple diagnostic strip test detects a water soluble antigen (histidine rich protein 2) produced by blood stages of *P falciparum* . The test is simple and rapid.

High sensitivity and specificity have been reported in endemic areas. A pink band indicates a positive result. It requires no special training.

This study compared the new test with standard blood film microscopy in 160 febrile travelers returning to the UK from endemic areas. In 45, malaria was the final diagnosis. 42 were detected by microscopy, and 42 by *Parasight F*. The test was negative in one patient with low parasitemia malaria.

Predictive value of a positive test = 96%; predictive value of a negative test = 97%.

The test does not remove the need for blood film examination, as it is not 100% sensitive at low degrees of parasitemia. Repeat daily testing may be necessary to establish the diagnosis. Nor does the test give any indication of the density of parasites, which is essential for planning management. It may used to distinguish between more benign malarias and the potentially lethal falciparum.

It has a useful role in initial screening.

BMJ August 19-26 2000; 321: 484-85 Original investigation, first author I M Cropley, Northwick Park Hospital, Middlesex, UK [www.bmj.com/cgi/content/full/321/](http://www.bmj.com/cgi/content/full/321/)

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### **8-21 RACECADOTRIL IN THE TREATMENT OF ACUTE WATERY DIARRHEA IN CHILDREN.**

1. *Enkephalins* occur naturally in the gut. They act in the gi tract by activating opioid receptors. This results in reduced secretion of water and electrolytes.

2. *Enkephalinase* is an enzyme that inactivates enkephalins and thus counteracts their action.

3. *Racecadotril* (acetorphan) is an enzyme inhibitor. It inhibits enkephalinase. Thus the action of the normally occurring enkephalins is preserved. Improvement in diarrhea follows. It has antisecretory actions only when hypersecretion is present, not in the basal state.

This study assessed whether oral racecadotril in addition to oral rehydration therapy would be more effective treatment than oral rehydration therapy alone. Over 130 boys age up to 3 years were randomized. All had watery diarrhea due mainly to rotavirus. All were dehydrated and hospitalized. None had bloody diarrhea.

The racecadotril group had significantly less stool output in the first 48 hours. Median duration of diarrhea was reduced (28 hours vs 72 hours). Intake of oral rehydration solution was significantly less.

The investigators concluded that racecadotril combined with oral rehydration was safe and effective. It may be especially welcome therapy in developing countries.

Opiate drugs currently used (eg, loperamide) also act largely by activating an opiate receptor in the gut — but a different receptor. Their action disrupts peristalsis. Racecadotril does not affect motility of the gut.

NEJM August 17, 2000; 343: 463-67 Original investigation, first author Eduardo Salazar-Lindo, Hospital National Cayetano Heredia, Lima, Peru. [www.nejm.com](http://www.nejm.com)

Comment:

I do not know if this will turn out to be a practical application. I abstracted the paper because it is an example of the cutting edge of therapy. Before this, I had never heard of enkephalins occurring in the gut. RTJ

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