

PRACTICAL POINTERS
FOR
PRIMARY CARE
ABSTRACTED MONTHLY FROM THE JOURNALS
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LIFESTYLE CHANGES TO PREVENT TYPE 2 DIABETES

EXERCISE WITHOUT WEIGHT LOSS BENEFITS TYPE 2 DIABETES

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SPIRONOLACTONE REDUCES PROTEINURIA IN CHRONIC RENAL DISEASE

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HIGHLIGHTS SEPTEMBER 2001

9-1 DIET, LIFESTYLE, AND THE RISK OF TYPE 2 DIABETES MELLITUS IN WOMEN.

Most cases of type 2 diabetes could be prevented by a healthy lifestyle: weight control, regular exercise, modification of diet, abstinence from smoking, and limited consumption of alcohol.

Weight control would appear to offer the greatest benefit.

9-2 EFFECTS OF EXERCISE ON GLYCEMIC CONTROL AND BODY MASS INDEX IN TYPE 2 DIABETES MELLITUS

Exercise programs per se, both resistance and aerobic, over a 4 month period resulted in a reduction in HbA1c of a magnitude likely to be of clinical significance. .

Practical points:

- A. Exercise improved HbA1c, not dependent on weight loss.
- B. Resistance exercise was also of value, especially applicable to patients who cannot walk.
- C. Patients can be told as little as 4 months of consistent exercise 3 to 4 times weekly will benefit.
- D. Exercise per se is likely to be beneficial in preventing development of type 2 diabetes in patients with impaired glucose tolerance or elevated fasting glucose levels not now considered as having type 2 diabetes.

9-3 INSULINS TODAY AND BEYOND

"Insulin glargine (*Lantus*) as the basal insulin combined with rapid acting analogues (*Humalog*) is probably the most physiological insulin substitution therapy and will therefore be the basis for future comparisons."

Practical point: In difficult-to-control diabetics, the combination will more likely reduce the HbA1c toward normal.

9-4 PERIPHERAL ARTERIAL DISEASE DETECTION, AWARENESS, AND TREATMENT IN PRIMARY CARE.

PAD is prevalent in older Americans. It is associated with a high risk of cardiovascular complications. Many patients are not diagnosed before occurrence of a morbid event.

PAD is easily detected with the ankle/brachial index (ABI) in primary care.

Treatment of hypertension, lipid disorders, and diabetes are as important in patients with PAD as in patients with coronary disease. Smoking cessation is essential.

Practical point: Should all primary care clinicians make ABI available? Yes, but not necessarily in their own offices. But, primary care clinicians should institute preventive measures far before the ABI becomes abnormal.

9-5 ASPIRIN USE AND ALL-CAUSE MORTALITY AMONG PATIENTS BEING EVALUATED FOR KNOWN OR SUSPECTED CORONARY ARTERY DISEASE. A Propensity Analysis

Aspirin use among patients suspected of CAD was independently associated with reduced long-term all-cause mortality, particularly among older patients, those with known CAD, and those with impaired exercise capacity.

Practical point: Prophylactic low-dose aspirin will benefit individuals at higher risk of CVD. For those at low risk, harms outweigh benefits. The challenge for primary care clinicians is to judge the risk.

9-6 CHALLENGE OF CULTURE, CONSCIENCE, AND CONTRACT TO GENERAL PRACTITIONER'S CARE OF THEIR OWN HEALTH: Qualitative Study

Doctors perceive that their professional position and training adversely influence their attitudes to illness in themselves and their colleagues..

The list of doctor's duties begins with "make the care of your patient your first concern". The authors of this study suggest that a duty of self knowledge and self care should underpin this. Organizational changes within practice must take account of the barriers experienced in accessing physician health care. Medical education and culture should strive to promote appropriate self care among doctors.

Practical point: "Physician, heal thyself."

9-7 HELICOBACTER INFECTION AND THE DEVELOPMENT OF GASTRIC CANCER

Gastric cancer developed in patients infected with *H pylori*, but not in uninfected patients.

Gastric cancer did not develop in any of the infected patients who received eradication therapy.

Patients with duodenal ulcers were not at risk.

Evidence is accumulating that eradication therapy is effective in prevention of gastric cancer. "Gastric cancer may in the future be viewed, like colon cancer, as largely a preventable disease." "We may need to view *H pylori* less as a beneficial commensal organism, and more as something akin to tobacco."

Practical point: *H pylori* infections should be eradicated.

9-8 RANDOMIZED TRIAL OF A PERINDOPRIL-BASED BLOOD-PRESSURE-LOWERING REGIMEN AMONG 6105 INDIVIDUALS WITH PREVIOUS STROKE OR TRANSIENT ISCHAEMIC ATTACK.

In patients with previous stroke or TIA, a combination of an ACE inhibitor and a diuretic lowered mean BP from about 148/86 to about 125/75 and resulted in a large reduction in risk of recurrence of stroke.

"Treatment . . . should be considered routinely for patients with a history of stroke or TIA, irrespective of their BP."

Importantly, benefit for BP lowering was evident in patients not usually considered to be hypertensive — ie, those with "high normal" BP in whom BP was lowered from a mean of 136/79 to 127/75.

Practical point: A reduction to about 125/75 would benefit without causing harm.

9-9 THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES.

In patients with type 2 diabetes, microalbuminuria, and hypertension, the angiotensin II blocker, irbesartan, was renoprotective, independent of its blood pressure lowering effect

Choice of an ACE inhibitor vs an angiotensin II blocker would depend on adverse effects (eg, cough) and cost.

Practical point: All patients with diabetes should be tested for microalbuminuria. Treatment with an ACE inhibitor or an angiotensin blocking drug should be started early.

9-10 BENEFICIAL EFFECTS OF POTASSIUM: Clinical Review

There is good evidence that potassium (K) intake is important in regulating blood pressure. Increasing K intake lowers BP in both hypertensive and normotensive patients.

This review article discusses other probable benefits of increased K intake: Lowering risk of stroke; prevention of renal vascular, glomerular, and tubular damage; reduction of urinary calcium excretion, possibly reducing stone formation and preventing bone demineralization; and reduction in risk of ventricular arrhythmias in patients with ischemic heart disease, heart failure, and left ventricular hypertrophy.

Practical point: The best way to increase K intake is to eat more fresh fruit and vegetables.

9-11 BLOOD LIPID CONCENTRATIONS AND RISK OF MYOCARDIAL INFARCTION

As in the West, Algerians who survived a MI, had higher total cholesterol and LDL-cholesterol, and lower HDL-cholesterol than controls. However, concentrations rarely reached the levels usually considered when instituting treatment in Western countries. The ratio of total-c/HDL-c, and of

LDL-c/HDL-c, as in the West were similarly elevated. These ratios are therefore good predictors of risk, irrespective of nationality.

Practical point: A ratio has greater predictive value than total-cholesterol or LDL-cholesterol alone. Total cholesterol levels alone may be very misleading.

9-12 TINZAPARIN IN ACUTE ISCHEMIC STROKE (TAIST): A Randomized, Aspirin-controlled Trial

Treatment with the low-molecular weight heparin, tinzaparin, within 48 hours of acute ischemic stroke did not improve functional outcome compared with aspirin. It was associated with increased intracerebral hemorrhage.

Practical point: Rely on aspirin alone

9-13 LONG-TERM WEIGHT LOSS WITH SIBUTRAMINE

Sibutramine administered for 48 weeks resulted in clinically relevant weight loss compared with placebo.

Practical point: Although possibly of long term benefit, this therapy should be left to specialists.

9-14 METFORMIN IN NON-ALCOHOLIC STEATOHEPATITIS

In patients with steatohepatitis, metformin given over 4 months reduced ALT, increased insulin sensitivity, and decreased liver size.

Practical point: Primary care clinicians will encounter patients with steatohepatitis. Most will be secondary to alcoholism, obesity, or diabetes. Metformin may benefit a subset.

9-15 EFFECT OF LEVODOPA IN COMBINATION WITH PHYSIOTHERAPY ON FUNCTIONAL MOTOR RECOVERY AFTER STROKE

The brain is plastic. It is pliable and capable of being reformed. Specific transmitters are involved. Enhancement of functional motor recovery seems to rely on an increased concentration of norepinephrine at the synapses.

Levodopa is converted to dopamine in the brain. Small amounts are then converted to norepinephrine.

Combined with physiotherapy, levodopa was an effective and safe method for improving motor recovery after stroke. In view of its minimal side effects, it will be a possible add-on during stroke rehabilitation.

Practical point: None at this time. I abstracted this study because it is so provocative. Watch for follow-ups.

9-16 ROLE OF INFLAMMATORY BIOMARKERS IN PREDICTION OF CORONARY HEART DISEASE.

C-reactive protein, is a strong and independent predictor of future vascular events. Measurement of this inflammatory marker adds to the predictive value of standard lipid screening, particularly in primary prevention. The greater prognostic utility of C-reactive protein reflects the long half-life and stability of the molecule. This is coupled with a lack of circadian variation and low coefficients of variation when measured by high sensitivity assays.

Practical point: CRP has not yet been included in the usual risk markers. CRP is of potential future interest. We await clarification. Primary care clinicians — keep it in mind.

9-17 PEGINTERFERON ALFA-2B PLUS RIBAVIRIN COMPARED WITH INTERFERON ALFA-2B PLUS RIBAVIRIN FOR INITIAL TREATMENT OF CHRONIC HEPATITIS C

The most effective therapy for patients with chronic hepatitis C was peginterferon (a new compound of interferon with polyethylene glycol) once weekly combined with oral ribavirin. The benefit was mainly in patients with type 1 infection.

Practical point: The prevalence of hepatitis C is high. Primary care clinicians should be able to refer patients for the best therapy.

9-18 SEVERE PULMONARY EMBOLISM ASSOCIATED WITH AIR TRAVEL

The greater the distance and time traveled in airflights the greater the risk. The absolute incidence is low.

Almost all patients had high and moderate risk of thromboembolic disease.

The sitting position is associated with venous stasis. The double 90-degree angle bends at the knee and hip impede flow.

Practical point: Simple behavioral and mechanical prophylaxis should be considered to prevent air-travel associated PE and DVT, especially in patients with risk factors.

9-19 SPIRONOLACTONE IN ADDITION TO ACE INHIBITION TO REDUCE PROTEINURIA IN PATIENTS WITH CHRONIC RENAL DISEASE

The study entered eight patients with various renal diseases and persistent proteinuria despite treatment with enalapril (*Vasotec*) for 12 months. Spironolactone 25 mg daily was then added.

After treatment, there was a mean 54% reduction in protein excretion. There was no significant reduction in BP or creatinine clearance.

"Spironolactone therapy may be useful in patients with proteinuria and renal impairment who still have proteinuria after treatment with ACE inhibitors."

Practical point: Spironolactone add-on may be helpful in some patients with renal disease as well as in some with heart failure.

Primary prevention of type 2 diabetes.

9-1 DIET, LIFESTYLE, AND THE RISK OF TYPE 2 DIABETES MELLITUS IN WOMEN.

This study examined a set of dietary and environmental factors in relation to risk of developing type 2 diabetes. It estimated the proportion of cases that could theoretically be avoided through the simultaneous adoption of multiple types of low-risk behavior.

Conclusion: The majority of cases of type 2 diabetes could be prevented by the adoption of a healthier lifestyle.

STUDY

1. The Nurses' Health Study followed over 84 000 female nurses from 1980 to 1996. All were free of diagnosed cardiovascular disease, diabetes, and cancer at baseline.
2. Obtained information about diet and lifestyle, updated regularly, and development of type 2 diabetes.
3. Defined a low-risk group according to a combination of variables: 1) body mass index less than 25; 2) diet high in cereal fiber and polyunsaturated fat, low in trans fat, and low in glycemic load (effect of specific foods on the blood glucose level); 4) engagement in moderate-to-vigorous physical activity for at least 1/2 hour a day; 5) no current smoking; and 6) consumption of at least half a drink of alcoholic beverage per day.

RESULTS

1. Documented 3300 new cases of type 2 diabetes during 16 years of follow-up.
2. Overweight was the single most important predictor of diabetes. Relative risk of diabetes was 39 for women with a BMI over 35, and 20 for those with a BMI 30-35. A BMI at the high end of the normal range (23 to 25) was associated with a risk of 2.7 relative to those with BMI < 23.
3. Lack of exercise, a poor diet, current smoking, and abstinence from alcohol use were all associated with significantly increased risk, even after adjustment for body mass index.
4. Of interest, the association between diabetes and diet, physical activity, smoking, and alcohol use was generally similar among overweight and obese women as among those with a normal BMI. (I.e, risk factors increased risk of development of type 2 diabetes even in those not considered obese.)

5. Compared with the rest of the cohort, women in the low-risk group (3.4% of women) had a relative risk of diabetes of 0.09. (Ie, those with no risk factors were at extremely low risk.)
6. The population "attributable risk" in this population was 87% — ie, 87% of new cases might have been prevented if all women had been in the low risk category. The population attributable risk increased to 91% when abstinence from smoking and use of small amounts of alcohol were included.
7. Individual components of the diet were independently and significantly associated with risk. (Ie, increased cereal-fiber intake and increased polyunsaturated fat/saturated fat ratio reduced RR; increased trans fat and increased glycemic load both increased risk.)
8. Women in the low risk of 3 categories (BMI, diet, and exercise) has a RR of 0.12 compared with all women.
9. The reduction in risk associated with the low risk factors was similar in women with a family history as well as for those without.
10. Even among obese women (BMI > 35) a combination of a healthy diet and regular exercise was associated with a 24% reduction in risk. (Ie, even if weight was maintained.)
11. If a BMI of 23 were to be adopted as the high end of the normal range, the population attributable risk of developing diabetes would have been reduced to 2.3%.

DISCUSSION

1. In middle-aged women, a combination of favorable lifestyle factors was associated with an incidence of type 2 diabetes that was about 90% lower than incidence in women without these factors. "The majority of cases of type 2 diabetes could be avoided by behavior modification."
2. Weight control would be the most effective way to reduce risk. "The public does not recognize the connection between overweight and diabetes." Greater educational efforts are needed.
3. Adoption of diet and exercise by obese women would result in an absolute reduction in incidence of diabetes even if they do not lose weight.

CONCLUSION

Most cases of type 2 diabetes could be prevented by a healthy lifestyle: weight control, regular exercise, modification of diet, abstinence from smoking, and limited consumption of alcohol.

Weight control would appear to offer the greatest benefit.

NEJM September 13, 2001; 3345: Original investigation, first author Frank B Hu, Harvard School of Public Health, Boston, Mass. www.nejm.org

Comment:

Lifestyle changes result in primary prevention. In patients with established type 2 diabetes, the same measures decrease severity of the disease (secondary prevention) and may, in some patients, "cure" the disease. (Ie, improve glucose tolerance enough to remove them from being defined as "diabetic".

Exercise beneficial even without weight loss

9-2 EFFECTS OF EXERCISE ON GLYCEMIC CONTROL AND BODY MASS INDEX IN TYPE 2 DIABETES MELLITUS

Reduction of hyperglycemia and body fat are major goals of diabetes therapy. Obesity, especially abdominal obesity, is associated with insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia, and hypertension. These abnormalities tend to cluster and are referred to as the “metabolic syndrome”. Regular exercise in non-diabetic subjects has beneficial effects on virtually all aspects of the syndrome.

This study was designed to guide clinicians in recommending exercise plans for their patients with diabetes.

Conclusion: Exercise training reduced HbA1c significantly even in patients who did not lose weight.

STUDY

1. Literature search systematically selected and reviewed 14 trials on the effect of exercise in adults with type 2 diabetes. Studies that included drug co-interventions were excluded.
2. Types of exercise:
 - A. Aerobic training studies (n = 12): Moderate exercise sessions for a mean of 50 minutes, three to 4 times a week for 18 weeks
 - B. Resistance training studies (n = 2): Mean of 10 exercises with 13 repetitions 3 times weekly for 15 weeks.
3. Compared baseline and post-intervention data in intervention and control groups.

RESULTS

1. At 4 months, mean HbA1c was lowered in the intervention groups to 7.65% vs 8.31% in controls .
2. Aerobic and resistance exercise reduced HbA1c similarly.
3. Difference in post-intervention body mass in the exercise groups vs control groups was not statistically significant (83.02 kg vs 82.48 kg). (Ie, essentially little or no weight loss.)

DISCUSSION

1. Exercise was associated with a significant reduction in HbA1c. Body mass was not changed.

The improvement in HbA1c was not dependent on weight loss. “The finding that exercise does not need to reduce body weight to have a beneficial impact on glycemic control is clinically important.”
2. The investigators believe a reduction in HbA1c of this magnitude (0.66%) is related to a significant reduction in diabetes-related clinical endpoints.
3. Unlike insulin and sulfonylureas, exercise is associated with other cardioprotective benefits without causing weight gain.

4. Exercise training decreases hepatic and muscle insulin resistance and increases glucose disposal. This would not necessarily depend on weight change.
5. It is possible that one reason for the maintenance of weight might be a result of increased muscle mass and decreased fat mass.
6. These results are widely generalizable to middle-aged patients with type 2 diabetes.

CONCLUSION

Exercise training over 4 months reduced HbA1c by a mean of approximately 0.7%. This would be expected to reduce risk of diabetic complications. Exercise should be considered beneficial in itself, and not merely as an avenue to weight loss.

JAMA September 12, 2001; 286: 1218-27 Original investigation, first author Normand G Boule, University of Ottawa, Canada www.jama.com

Comment:

This study adds several important clinical points. Patients can be informed that: Exercise per se improves glucose tolerance aside from any effect on weight. (However, the combination of exercise + diet + weight loss + drugs would likely be even more beneficial.) Resistance exercise is of value, especially for patients who cannot walk, or when added to walking. As little as 4 months of consistent exercise 3 to 4 times weekly will benefit. Results of this study might increase adherence when patients realize the benefits.

Exercise per se is also likely to be beneficial in *preventing* development of type 2 diabetes in patients with glucose intolerance or impaired fasting glucose levels.

REFERENCE ARTICLE

9-3 INSULINS TODAY AND BEYOND

Achieving and sustaining near-normoglycemia is required to delay onset and retard progression of diabetic angiopathy. Physiological insulin replacement is central to management. Insulin formulations, treatment strategies, and methods and routes of delivery have changed. More options are available for monitoring effects of insulins on blood glucose for safety and optimum control. Nevertheless, premature vascular complications are a constant reminder that management strategies are, for most patients, still inadequate.

The review begins by illustrating the normal 24-h plasma glucose and insulin profiles. Normally, despite wide fluctuations in nutritional intake, glucose concentrations remain within a narrow range throughout the day. (3.5 to 7.0 mmol/L; 63 to 126 mg/dL). After eating, plasma glucose rises to peak at 30-60 minutes. It returns to basal concentrations within 2 to 3 hours. Plasma insulin has a similar pattern.

In the fasting state, rates of endogenous glucose production and use are almost equal.

There are now about 180 branded insulin preparations available worldwide. Striking differences in prescribing habits are seen both within and between countries. Replacement of physiological insulin and return of glucose to near-normal concentrations remain elusive goals. A bolus subcutaneous injection of soluble (regular) human insulin results in a plasma-insulin profile that is very different from the normal postprandial plasma-insulin response seen in individuals without diabetes. After injection, an initial delay is followed by an increase in plasma insulin that peaks at 1 to 2 hours and returns to basal within 6 to 8 hours. This contrasts with the rapid and short-lived prandial insulin response seen in persons without diabetes.

Absorption of insulin injected into subcutaneous tissues differs between and within individuals. The dose, site of administration, concentration of the insulin, and blood supply all contribute to rate of absorption. This is another factor which results in variation of the plasma-insulin response.

Now recombinant DNA technology is used to produce new insulin analogues which overcome some of these difficulties. Short-acting insulin lispro and long-acting insulin glargine are now available.

INSULIN LISPRO

Insulin lispro (*Humalog*) is more rapidly absorbed from subcutaneous tissue and is active for a shorter time than is soluble (regular) human insulin. When injected immediately before food, insulin lispro consistently restricts postprandial glucose fluctuations much more than human soluble insulin given up to 30 minutes before start of a meal. Their antihyperglycemic effect is equivalent. The analogue shows less variability in absorption. It is associated with a reduction in number of episodes of nocturnal hypoglycemia.

Because insulin lispro suppresses the glucagon response more quickly than soluble insulin, restoration of the early rise in prandial insulin concentration inhibits the early rise in prandial hepatic glucose output, thereby lowering postprandial glucose concentration. This spares beta-cell function.

Insulin lispro provides the convenience of administration immediately before the meal. (The recommended administration of soluble insulin is 15 to 30 minutes before meals. This is largely ignored by patients.) Quality of life is improved by the increased flexibility of lifestyle and lower risk of hypoglycemia. However, to achieve satisfactory preprandial and postprandial glycemia, the interval should account for the preprandial glucose since it might be necessary to give the analogue 15 to 30 minutes before eating in patients who are greatly hyperglycemic.

In gestational diabetes, insulin lispro provides better control and results in fewer hypoglycemic events than does soluble insulin. The need to return the 1-hour postprandial glucose to normal to improve fetal outcome makes lispro especially suitable for use in pregnancy. No adverse effects on the fetus have been recorded. This is fast becoming accepted practice, although pregnancy is not yet an approved indication for use of insulin lispro. .

Due to late postprandial and nocturnal hyperglycemia which occurs when insulin lispro is used, substantial improvement in HbA1c is seen only when basal insulin is replaced. With the exception of a reduction in nocturnal hypoglycemia, insulin lispro has not improved glycemic control in most patients. We need a more physiological basal insulin supplementation to achieve improved overall glycemic control without producing hypoglycemia.

In patients taking intermediate-acting insulins (NPH; protamine zinc), rates of absorption from subcutaneous injections vary. Both human NPH and ultralente insulins fail to adequately and consistently provide 24-h basal requirements. The need for increased basal (overnight) insulin was recognized when insulin lispro given by continuous subcutaneous injection lowered HbA1c concentrations. Long-term sustainable improvements in glycemic control with less day to day fluctuations and a lower frequency of hypoglycemia is achieved by combinations of insulin lispro with NPH insulin at meal times. This suggests need for a better long-acting insulin.

INSULIN GLARGINE

Insulin glargine (*Lantus*) is an insulin analogue which has a much slower and more reproducible rate of absorption than NPH. Its onset is slower and the effect on glycemia is extended. Insulin glargine plateaus at a concentration 2 to 3 times lower than NPH within 6-8 hours and remains essentially unchanged for 24 h. It is unaffected by the site of injection. Studies have reported that insulin glargine given at bedtime at the same dose as NPH, results in a greater reduction in fasting glucose, less variability in blood glucose, a lower frequency of nocturnal hypoglycemia, and a fall in HbA1c. The dawn rise in glucose is suppressed by insulin glargine. There is also no weight gain, or less weight gain than with NPH.

"Insulin glargine as the basal insulin combined with rapid acting analogues (eg, lantus) is probably the most physiological insulin substitution therapy and will therefore be the basis for future comparisons." Evidence of safety has clearly satisfied the regulatory authorities.

CONCLUSION

Until recently, available insulin preparations made it almost impossible to achieve good control without considerable disruption of life-style. Recombinant DNA technology has made it possible to design insulins with improved pharmacokinetics to better provide prandial (bolus) and basal insulin needs. The combination of rapid acting and long-acting analogues helps to more accurately approximate normoglycemia without causing hypoglycemia.

Lancet September 1, 2001; 358: 739-46 Review article, first author David R. Owens, Llandough Hospital, Penarth, Wales, UK www.thelancet.com

9-4 PERIPHERAL ARTERIAL DISEASE DETECTION, AWARENESS, AND TREATMENT IN PRIMARY CARE.

Peripheral arterial disease (**PAD**) is a highly prevalent atherosclerotic syndrome. It is associated with high rates of myocardial infarction, stroke, and other thromboembolic events as well as increased mortality and decreased quality of life.

Despite its prevalence and importance, PAD is underdiagnosed, and patient awareness of PAD and its consequences is low. PAD has not emerged as a focus of public health efforts to improve quality of life nor to decrease the associated risk of cardiovascular disease. PAD is undertreated.

The "PAD Awareness, Risk and Treatment: New Resources for Survival (PARTNERS) Program" is a national investigation assessing the feasibility of detecting PAD using the ankle/brachial index (**ABI**) in office based practice.

Conclusion: Prevalence of PAD is high. Awareness is low. A simple ABI measurement identifies patients and allows treatment.

STUDY

1. Multicenter, cross-sectional study conducted at 27 sites in the US entered over 6900 individuals.
2. All were over age 70 or age 50-69 with a history of cigarette smoking or diabetes.
3. Measured ankle/brachial index (ratio of systolic blood pressure at the ankle to systolic blood pressure at the brachial artery). Systolic blood pressures were recorded with the aid of Doppler ultrasound at both brachial arteries and all 4 ankle-foot arteries. Sensitivity of ABI of 0.9 or less is 90% and specificity is 98% for an angiographically defined stenosis of 50% or more in a major leg artery. (Ie, of all persons *with* arterial stenosis, 90 out of 100 will have an abnormal ABI; for all persons *without* arterial stenosis, only 2 out of 100 will have an abnormal ABI.)
4. Subjects were considered to have PAD if their ABI was 0.9 or less. (Eg, brachial systolic = 150; ankle systolic = 135. $150/135 = 0.9$) A systolic under 135 would indicate an abnormal ABI when present in either ankle or foot.

RESULTS

1. PAD was present in 29% of the cohort of 6000. Of these, 44% had PAD only without evidence of cardiovascular disease (**CVD**); 56% had combined PAD and CVD. A high percentage were women, almost all postmenopausal. Mean ABI in patients with PAD was 0.78
2. Overall:

PAD only	13%
PAD + CVD	16%
CVD only	24%
Neither	47%
3. In almost half of the patients PAD was newly diagnosed. Only about half of their physicians were aware of the PAD.
4. Classic intermittent claudication was distinctly uncommon.
5. Patients with PAD had similar atherosclerotic risk factors compared with those with CVD.
6. Antiplatelets were not often prescribed.

DISCUSSION

1. PAD is prevalent in primary care settings and confers a high risk of associated fatal and non-fatal cardiovascular ischemic events.

2. It is easily detected by ABI measurement during routine office visits. (*History and physical examination are inaccurate detectors of PAD.*)
3. Clinicians who rely on intermittent claudication to diagnose PAD will miss most patients with PAD.
4. Even in patients without established CVD, an ABI of 0.78 portends an approximate 30% 5-year risk of MI, stroke, and vascular death.
5. Smoking cessation reduces disease progression and mortality risk in PAD patients.
6. The diagnosis of diabetes is adequate to initiate prophylactic treatment in almost all patients regardless of evidence of PAD.
7. Guidelines for treatment of hypertension recognize that if PAD is present, drug therapy for all stages of hypertension is required.
8. Antiplatelet therapy is recommended for secondary prevention (ie, in those with ABI < 0.9).¹

CONCLUSION

PAD is prevalent in older Americans. It is associated with a high risk of cardiovascular complications. Many patients are not diagnosed before occurrence of a morbid event.

PAD is easily detected with the ABI in primary care.

Treatment of hypertension, lipid disorders, and diabetes is as important in patients with PAD as in patients with coronary disease. Smoking cessation is essential.

JAMA September 19, 2001; 286: 1317-24 Original investigation by the PARTNERS group, first author Alan T Hirsch, University of Minnesota Medical School, Minneapolis. www.jama.com

Comment

The average *normal* ABI is somewhat over 1.0 (Ie, ankle BP > brachial BP. In this study mean *abnormal* ABI was 0.78

Should all primary care clinicians make ABI available? Yes, but not necessarily in their own offices. Some subsets of primary care health care workers (eg, nurses; technicians) would be able to perform the test with more efficiency and accuracy.

This is an interesting and important edemiological study. It, however, judges the wrong end of the stick. Primary care clinicians should focus on primary prevention, not on diagnosis and treatment. The same preventive measures apply to PAD as to other cardiovascular diseases. It is much more productive to prevent a teenager from beginning smoking than it is to try to get a 70-year old to stop.

1 In this study of patients over age 50 at high risk and unselected patients over age 70, almost half had PAD and/or CVD. It seems to me that any disease of this prevalence would demand universal prevention. Would not near universal use of prophylactic, low-dose aspirin be a reasonable recommendation, even in women?

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9-5 ASPIRIN USE AND ALL-CAUSE MORTALITY AMONG PATIENTS BEING EVALUATED FOR KNOWN OR SUSPECTED CORONARY ARTERY DISEASE.

A Propensity Analysis

This was my introduction to propensity analysis. What is it? My dictionary defines propensity as an innate inclination, tendency, or bent. Simply stated, in a case-control study, propensity analysis attempts to match from a large number of controls the subset of subjects who are most like the case subjects. It goes far beyond the usual matching of sex, age, and geographical location. In this study, aspirin users and non-users were matched by about 30 baseline characteristics. This reduced the chance of selection bias.

Aspirin has been shown to reduce cardiovascular morbidity and mortality following acute myocardial infarction.

This study asks – What is the association between aspirin use and long-term, all-cause mortality?

Conclusion: Among a group of patients with suspected coronary artery disease (**CAD**), aspirin use was associated with a reduction in long-term all-cause mortality.

STUDY

1. Prospective, nonrandomized observational trial entered 6174 patients. All had been referred for echocardiography because of known or suspected CAD.
2. Over 2310 (37%) were taking aspirin regularly. After excluding patients with significant valvular disease, documented contraindications to aspirin (including peptic ulcer), renal insufficiency, and NSAID use, 1351 subjects remained.
3. Of the 3864 non-aspirin users (controls), 1351 were selected on the basis of being the most comparable to the aspirin users. 30 clinical characteristics were used in the match.
(Table 3, p 1191)
4. Determined all-cause mortality according to aspirin use (n = 1351), or non-use (n = 1351), over 3-year follow-up.

RESULTS

1. Over 3 years, 276 (4.5%) of the cohort died.
2. In a simple univariate analysis (ie comparing all aspirin users with all non-aspirin users) there was no association between aspirin use and mortality. (4.5% vs 4.5%)
3. Comparing the two groups selected by propensity analysis, the 1351 patients taking aspirin had a mortality of 4%; 1351 non-aspirin users had a mortality of 8%.
4. The patient characteristics associated with the greatest aspirin-related reductions in mortality were: older age, known CAD, and impaired exercise capacity.

DISCUSSION

1. Among consecutive patients referred because of suspected CAD, aspirin use was associated

with a substantial reduction in all-cause mortality.

2. The consecutive patients in this study may represent a more representative sample of real world patients than those selected to enter into a randomized, controlled trial.
3. The findings provide additional support for recommending the routine use of aspirin in patients at risk for cardiovascular disease.

CONCLUSION

Aspirin use among patients suspected of CAD was independently associated with reduced long-term all-cause mortality, particularly among older patients, those with known CAD, and those with impaired exercise capacity.

JAMA September 12, 2001; 286: 1187-94 Original investigation, first author Patricia A Gum, Cleveland Clinic Foundation, Cleveland, Ohio. www.jama.com

Comment:

This is really a secondary prevention study. The case subjects (aspirin users) were more likely to have established coronary disease.

The NNT (benefit 1 patient over 3 years) = 25. This is a high benefit/harm-cost ratio, considering the safety and cost of aspirin and the high benefit (survival).

It supports prophylactic aspirin use for primary prevention.

"Doctor, heal thyself"

9-6 CHALLENGE OF CULTURE, CONSCIENCE, AND CONTRACT TO GENERAL PRACTITIONER'S CARE OF THEIR OWN HEALTH: Qualitative Study

"The health of the medical profession is causing some concern." Doctors are reluctant to seek health care through the usual mechanisms, and find it difficult to adopt the role of patient. The consequences include self prescription, working through illness, self referral, and late presentations with serious problems. This inappropriate self care occurs in a profession that reports high levels of stress, psychological distress, and comparatively high suicide rates.

This study explored general practitioners' perceptions of the effects of their profession and training on attitudes of illness in themselves and colleagues.

Conclusion: Doctors perceive that their professional position and training adversely influence their attitudes to their own illness.

STUDY

1. Qualitative study of 27 primary care physicians used focus groups and in depth interviews seeking views about their own health and that of colleagues.

RESULTS

1. Doctors were concerned about the current level of illness within the profession.
2. They described their need to portray a healthy image to both patients and colleagues. This hindered acknowledgement of personal illness and willingness to engage in health screening.
3. Embarrassment in adopting the role of patient and concerns about confidentiality also influenced their reaction to personal illness.
4. These attitudes can impede access to appropriate health care for themselves, their families, and their colleagues.
5. Almost all reported working through illness and expecting their colleagues to do likewise. This included illnesses they would not expect their patients to work through. A sense of conscience toward patients and colleagues and the working arrangements of the practice were cited as reasons.
6. Participants were reluctant to declare themselves ill, but readily shared anxieties about the health of the profession. "We are seeing increasing illness in doctors that's quite scary. It used to be 50 year olds with MIs, now they are seen in physicians in their 30s, along with various other stress-related illnesses."
7. There is pressure to appear well. This reflects the perception that patients believe a doctor's health reflects medical competence. The attitude affects their approach to screening. "Nobody wants to go and see a doctor who is sick."
8. Acknowledging psychological illness was extremely difficult. It was regarded as a weakness. Concerns about confidentiality emerged as a factor in use of psychiatric services. Embarrassment was a barrier to consulting other primary care physicians. "Doctors feel they shouldn't be sick. You don't want to go see your local psychiatrist in case one of your patients is sitting beside you."
9. Comments indicated a reluctance to accept treatment and an underlying assumption that the roles of patient and doctor were incompatible. "We think we're superhuman and that we don't get ill and that if we do, we can cope with it." Some reported that, in medical school and hospital, illness was not tolerated. "You were expected to do the job." Self care was not adequately taught. Several reported their medical knowledge made them prone to swing between panic and denial when they experienced symptoms. Similar stresses were described regarding illness in their family.
11. A sense of obligation to colleagues emerged. "You don't stay off work because you're not going to earn money, you continue to work because of your partners." "A terrible sense of duty of letting your partners down if you don't go in."
12. Most agreed that they did not take an active interest in their partner's health and played down evidence of colleagues being unwell.
13. The authors propose an "Informal Shadow Contract" (*page 730*) between individual clinicians and their partners which outlines how clinicians and partners should *not* respond to their illnesses.

CONCLUSION

Doctors perceive that their professional position and training adversely influence their attitudes to illness in themselves and their colleagues..

The list of doctor's duties begins with "make the care of your patient your first concern". The authors of this study suggest that a duty of self knowledge and self care should underpin this. Organizational changes within practice must take account of the barriers experienced in accessing health care. Medical education and culture should strive to promote appropriate self care among doctors.

BMJ September 29, 2001;323: 728-31 Original investigation, first author William T Thompson, Queen's University of Belfast, Ireland. www.bmj.com/cgi/content/full/323/7315/728

Comment: I'll bet that at least some of these points will hit the hearts of every primary care clinician. Self care includes primary prevention as well as secondary prevention. (See a preceding article on prevention of diabetes.) Doctors, as role models, should present a healthy lifestyle to their patients. RTJ

A potential primary preventive measure

9-7 HELICOBACTER INFECTION AND THE DEVELOPMENT OF GASTRIC CANCER

A higher risk of the development of gastric cancer has been reported in subjects with positive tests for *H pylori*. The WHO has reported there is sufficient epidemiological evidence to classify *H pylori* as a definite carcinogen. The rate of infection among patients with gastric cancer varies greatly among studies.

This study assessed the association.

Conclusion: In Japan, cancer developed in persons infected, but not uninfected persons.

STUDY

1. Prospectively studied over 1500 Japanese patients who had duodenal ulcers, gastric ulcers, gastric hyperplasia, or non-ulcer dyspepsia at the time of enrollment. None were taking NSAIDs. All underwent endoscopy with biopsy.
2. Of these, 81% had *H pylori* infection demonstrated by positive results of any one of 3 tests: serology, rapid urease, and histologic examination.
3. Follow up for a mean of 8 years in untreated patients; and a mean of 5 years after eradication in the treated patients.

RESULTS

1. Among 1526 patients, 1246 (81%) were *H pylori* positive. Gastric cancer developed in 3% of the infected patients; in none of the uninfected *patients*.
2. All those with active gastric ulcer, all those with gastric hyperplastic polyps, and all those with

active duodenal ulcer were infected with *H pylori*.

3. Risks differed among those with various clinical conditions at baseline:
 - Of 445 patients with non-ulcer dyspepsia, 21 (4.7%) developed gastric cancer over 8 years:
 - Of 297 patients with gastric ulcers, 10 (3.4%) developed cancer.
 - Of 229 patients with gastric hyperplastic polyps, 5 (2.2%) developed cancer.
 - Of 275 patients with duodenal ulcer, none developed cancer.
4. Among the infected patients, those with severe gastric atrophy, corpus-predominant gastritis, and intestinal metaplasia were at significantly higher risk for gastric cancer.
5. About 40% of those with non-ulcer dyspepsia were not infected. This was the only group that contained patients without infection.
6. Gastric cancer did not develop in any of 253 infected patients who received eradication therapy.

DISCUSSION

1. *H pylori* infection was associated with severe atrophic gastritis, corpus-predominant gastritis, and gastric intestinal metaplasia.
2. Gastric ulcer was associated with a high risk of gastric cancer; duodenal ulcer with low risk. Patients with gastric ulcers typically had corpus-predominant atrophic gastritis. Patients with duodenal ulcer had few atrophic changes and had antrum predominant gastritis. This may be the reason duodenal ulcer patients are at low risk of gastric cancer.
3. The authors previously had shown that in patients with early gastric cancer treated with endoscopic mucosal resection, eradication of *H pylori* prevents the development of a new cancer .

CONCLUSION

Gastric cancer developed in *patients* infected with *H pylori*, but not in uninfected patients.

Gastric cancer did not develop in any of the infected patients who received eradication therapy.

H pylori infection is associated with development of both intestinal-type and diffuse-type gastric cancer. Among infected patients, those with severe atrophy, accompanying intestinal metaplasia, corpus-predominant gastritis are at high risk for gastric cancer.

Patients with duodenal ulcers were not at risk.

NEJM September 13, 2001; 345: 784-89 Original investigation, first author Naomi Uemura, Kure Kyosai Hospital, Kure City, Japan www.nejm.org

Comment:

Although we may not be able to extrapolate risks from Japan to the US, I believe this strengthens the view of those who favor eradication in all patients with *H pylori* infection. RTJ

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HELICOBACTER PYLORI — NOT A GOOD BUG AFTER ALL

(This editorial comments and expands on a preceding study. [9-7])

"Worldwide, gastric cancer is the second most frequent cancer, and the second leading cause of death from cancer." The WHO classifies *H pylori* as a class I carcinogen. But whether anti-*H pylori* treatment reduces the long-term risk of gastric cancer is unknown.

"Many of the doubts about the link between *H pylori* and gastric cancer can now be put to rest." In the preceding study of Japanese subjects, gastric cancer developed in 3% of infected patients, but in none of the uninfected patients. Risk increased in all subgroups except those with duodenal ulcer.

This study, taken together with other studies, indicates that the association between *H pylori* and gastric cancer ranks with the association between smoking and lung cancer. In the case of well-differentiated, intestinal type gastric cancer, histopathological studies indicate that chronic *H pylori* infection progresses over decades through stages of chronic gastritis, atrophy, intestinal metaplasia, dysplasia, and cancer.

It is interesting that progression to atrophy, cancer, or both, in a patient with *H pylori* infection can be modulated by dietary salt. (Ie, salt acts as a facilitating agent.)

Why should duodenal ulcer be an apparent protective agent? Duodenal ulcer patients typically tend to have antrum predominant gastritis with increased parietal cell (acid producing) mass with a high level of acid production. This may prevent proximal migration of colonizing bacteria. This protects colonization of bacteria which may produce cancer facilitating nitrates.

In the study, patients with non-ulcer dyspepsia had the highest rate of cancer. Thus it can be argued that these patients should receive eradicating therapy on the basis of this risk alone. (Previous studies reported disappointing outcomes in relief of non-ulcer dyspepsia by eradication.) However, most patients with chronic *H pylori* infection have no symptoms. This raises questions about the need for population-based screening.

Evidence is accumulating that anti-*H pylori* therapy is effective in prevention of gastric cancer. "Gastric cancer may in the future be viewed, like colon cancer, as largely a preventable disease." "We may need to view *H pylori* less as a beneficial commensal organism, and more as something akin to tobacco.

NEJM September 13, 2001; 345: 829-32 Editorial, first author James G Fox, Massachusetts Institute of Technology, Cambridge. www.nejm.org

Primary prevention of stroke

9-8 RANDOMIZED TRIAL OF A PERINDOPRIL-BASED BLOOD-PRESSURE-LOWERING REGIMEN AMONG 6105 INDIVIDUALS WITH PREVIOUS STROKE OR TRANSIENT ISCHAEMIC ATTACK.

Among those who survive a stroke or a transient ischemic attack (TIA) the risk of further stroke is high. At least one in 6 suffers another stroke within 5 years.

Antiplatelet therapy reduces risk of stroke by about 20% among patients with an ischemic stroke or TIA. It is now prescribed routinely.

Carotid endarterectomy reduces the risk of recurrent ipsilateral stroke in those with carotid stenosis.

Anticoagulation reduces risk in those with atrial fibrillation.

No treatment has been proven to reduce recurrent risk of hemorrhagic stroke.

Observational studies have shown that BP levels are directly and continuously associated with the occurrence of ischemic stroke and cerebral hemorrhage. BP is an important determinant of risk of initial stroke in patients classified as not being hypertensive as well as in hypertensive patients

Systematic reviews of randomized trials of BP-lowering drugs in hypertensive patients without cerebrovascular disease (primary prevention) have shown that sustained BP reductions of about 5-6 diastolic reduce risk of initial stroke by about a third, with no large differences apparent between the main drug classes.

Studies of patients with a history of ischemic stroke (secondary prevention) suggested that BP reductions of about 6-8 systolic and 3-4 diastolic are associated with a fifth fewer recurrent strokes.

This present study assessed effects of a BP lowering regimen on non-hypertensive as well as hypertensive patients in secondary prevention of stroke.

Conclusion: BP lowering regimen using an ACE-inhibitor plus a diuretic reduced risk of recurrent stroke among non-hypertensive as well as among hypertensive patient.

STUDY

1. Randomized, double-blind, multicenter, secondary prevention study entered over 6100 patients (mean age = 64). All had a history of stroke (11% hemorrhagic), or TIA within the past 5 years. All were clinically stable.
2. All underwent a 2-week run in open-label period of 2 mg perindopril then 2 weeks of 4 mg. Those who adhered to, and tolerated, the run in were randomized.
3. Randomized to:
 - 1) An active treatment flexible regimen based on the ACE inhibitor perindopril (*Aceon*) 4 mg daily alone [single therapy] , or with addition of 2.5 mg of the non-thiazide diuretic indapamide (*Generic*) [dual therapy] at the discretion of the treating physician, or
 - 2) Placebo(s).
4. Most also received aspirin.
5. Primary outcome = total recurrent stroke (fatal and non-fatal). Follow-up = 4 years.

RESULTS

1. At baseline mean BP = 146/86. About half of the cohort was classified as "hypertensive" (BP \geq 160 and/or \geq 90)
2. Effect on BP overall (n = 6105):

Active treatment with perindopril alone (compared with placebo) reduced mean BP from 146/86 to 141/83.
Active treatment with perindopril plus indapamide reduced mean BP from 146/86 to 134/81.
These differences were maintained over the 4 years.
3. Effect on BP in subjects considered hypertensive [BP \geq 160/90; n = 2916]

Dual therapy reduced BP from a mean of 159/94 to 149/80

4. Effect on BP in subjects considered non-hypertensive [BP \leq 160/90; n = 3189]

Dual therapy reduced mean baseline BP from 136/79 to 127/75

5. Effect on risk of recurrent stroke:

Dual therapy (perindopril + diuretic) reduced risk of recurrent stroke by 43%.

But, single therapy with perindopril alone was associated with no discernable reduction of risk of recurrent stroke.¹

Both groups (hypertensive and non-hypertensive) achieved about equal benefit from dual therapy in reducing risk of recurrent stroke.

4. Dual therapy also was associated with a 26% reduction in major vascular events.

DISCUSSION

1. Dual therapy reduced annual stroke incidence from 3.8% to 2.4% (NNT 1 year = 71).

Results suggest that 5 years treatment with combination drugs would result in avoidance of one fatal or major non-fatal vascular event among every 11 patients. Absolute benefits of this size greatly exceed the estimated benefits of BP lowering for prevention of initial stroke in patients with uncomplicated hypertension.

2. There was a reduction in both recurrent fatal and disabling strokes (ischemic and hemorrhagic).
3. Importantly, benefit for BP lowering was evident in patients not usually considered to be hypertensive. Incidence of recurrent stroke was reduced not only among those with mean baseline BP 159/94, but also among those with a mean baseline BP of 136/79.
4. Benefits were achieved in the context of low withdrawal rate for adverse effects after initial screening for intolerance.
5. These results should resolve the clinical uncertainty that has existed about benefits and safety of BP lowering for patients with a history of stroke or TIA.
6. The HOPE study² also reported clear benefits with ACE inhibitor ramipril (*Altace*) for treatment of high risk, non-hypertensive patients as well as for those with hypertension.
7. The greater reduction in BP achieved by dual therapy would indicate that dual therapy is usually required for adequate BP reduction and that a reduction to about 130/80 would benefit without causing harm.
8. Treatment was safe across a broad range of patients irrespective of BP, type of qualifying cerebrovascular event, time since last event, or geographic region.. For patients presenting with an acute stroke or TIA, physicians should consider starting treatment early. Although treatment may commence with a single agent, the objective should be to move patients onto combination therapy as soon as possible.

CONCLUSION

In patients at high risk because of previous stroke or TIA, a combination of perindopril (an ACE inhibitor) and indapamide (a diuretic) lowered mean BP from about 148/86 to about 136/80 and resulted in a large reduction in risk

of recurrent stroke. Benefits were evident in those considered non-hypertensive (reduction in BP from baseline 136/79 to 127/75) as well as hypertensive patients.

"Treatment with dual therapy should be considered routinely for patients with a history of stroke or TIA, irrespective of their BP."

Lancet September 29, 2001; 358: 1033-41 Original investigation by the PROGRESS Collaborative Group, University of Sydney, Australia. "Perindopril Protection against Recurrent Stroke Study" www.thelancet.com

1 The reduction in BP by perindopril alone was sufficient to reasonably expect a benefit. The authors suggest the absence of benefit may have been due to chance.

2. "Heart Outcomes Prevention Evaluation Study Investigators." NEJM 2000; 342: 145-53 Effects of an angiotensin-converting-enzyme inhibitor ramipril, on cardiovascular events in high risk patients.

Comment:

To me, the remarkable finding was the benefit in the non-hypertensive group (reducing mean BP from 136/79 to 127/75). "Treatment with dual therapy should be considered routinely for patients with a history of stroke or TIA, irrespective of their BP." This reemphasizes the concept that risk of stroke rises continually as BP rises. There is no distinct cut point separating those at risk from those not at risk. For primary prevention, as well as secondary, we should strive for as low a BP as can be reasonably achieved in each individual. Any drug therapy should begin low and go slow. RTJ

A protective effect

9-9 THE EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES.

Microalbuminuria (20 to 200 ug per minute) and hypertension are risk factors for diabetic nephropathy. Blockade of the renin-angiotensin system by angiotensin-I-converting enzyme inhibitors (ACE-inhibitors) slows progression of nephropathy in patients with diabetes.

This study takes blockade one step farther. It examined the protective effect of an angiotensin-II-receptor antagonist (blockade at the cellular level) on development of nephropathy in hypertensive type 2 diabetic patients with persistent microalbuminuria.

Conclusion: Blockade of the receptor protected against development of nephropathy.

STUDY

1. Randomized, double-blind, placebo-controlled trial enrolled over 550 patients (mean age 58).

All had type 2 diabetes (WHO criteria). All had microalbuminuria (mean = 55 ug albumin / min) and hypertension (BP > 135/85; mean = 153/90). None had elevated creatinine levels.

2. Randomized to:

A. Irbesartan (*Avapro*) 300 mg daily, or

B. Placebo.

3. Primary end point = incidence of persistent albuminuria over 200 ug/min (diabetic nephropathy).
4. Follow-up = 2 years..

RESULTS

1. Five % of irbesartan group reached primary endpoint vs 15% in the placebo group.
2. Average BP = 141/83 in the irbesartan group vs 144/83 in the placebo group.
3. Serious adverse effects and withdrawals were less frequent in the irbesartan group than in the placebo group.

DISCUSSION

1. Treatment with irbesartan significantly reduced the risk of progression to clinical albuminuria, the hallmark of overt diabetic nephropathy.
2. The benefit appeared to be independent of blood pressure.
3. Kidney function remained well preserved in all groups.
4. Persistent albuminuria heralds progressive kidney disease ultimately leading to end-stage renal disease. An initial and sustained reduction in albuminuria during antihypertensive treatment is associated with a diminished rate of decline in the glomerular filtration rate and an improved prognosis.
5. The goal of delaying or preventing development of diabetic nephropathy can be achieved if high-risk patients are identified early and given appropriate renoprotective therapy.
6. "Routine screening for microalbuminuria should be performed in all patients with diabetes."
7. In the present study, there was no difference in glycemic control between groups. Metabolic factors cannot be considered to have played a part in the benefits of "sartan" therapy. Nevertheless, it must be emphasized that improvement in glycemic control slows the increase in the level of albuminuria and postpones the development of overt diabetic nephropathy.

CONCLUSION

In patients with type 2 diabetes and microalbuminuria the angiotensin II blocker, irbesartan, was renoprotective, independent of its blood pressure lowering effect.

NEJM September 20, 2001; 345: 870-78 Original investigation by the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group, first author Hans-Henrik Parving, Steno Diabetic Group, Copenhagen, Denmark.

www.nejm.org

Comment:

Two other studies in this issue of NEJM (pp 851-60 and pp 861-69) reported similar benefits from "sartan" drugs. The second, a study of losartan (*Cozaar*).

Review article

9-10 BENEFICIAL EFFECTS OF POTASSIUM: Clinical Review

There is good evidence that potassium (K) intake is important in regulating blood pressure. Increasing K intake lowers BP in both hypertensive and normotensive patients.

This review article discusses other probable benefits of increased K intake: lowering risk of stroke; prevention of renal vascular, glomerular, and tubular damage; reduction of urinary calcium excretion, possibly reducing stone formation and preventing bone demineralization; reduction in risk of ventricular arrhythmias in patients with ischemic heart disease, heart failure, and left ventricular hypertrophy.

The best way to increase K intake is to eat more fresh fruit and vegetables.

Does excess K intake have any harmful effects? K balance is normally maintained by precise mechanisms that match excretion to intake, mainly through the kidney. Large loads of K are excreted rapidly with only a minimal increase in plasma concentration. Severe renal disease may impair ability to excrete K. A concentration above 5.5 mmol/L is uncommon until over 90% of renal function is lost and the glomerular filtration rate is less than 20 mL/min. When renal function is impaired, increased K intake can aggravate hyperkalemia, although the greatest danger is when K is given intravenously.

Until recent years, humans consumed a diet low in sodium (< 10 mmol/d) and high in K (> 200 mmol/d). Now, the increasing consumption of processed foods which have K removed, and the reduction in fruit and vegetable intake, K intake has decreased (*and sodium intake increased*). The average consumption of K in Western countries is now about 70 mmol/d. The population would benefit from an increase in K intake.

BMJ September 1, 2001; 323: 497-501 “Clinical review” by Feng J He and Graham A MacGregor, St. George’s Hospital Medical School, London UK. www.bmj.com/cgi/content/full/323/7311/487

Comment;

This is a possible mechanism, at least in part, for the reported risk reductions associated with intake of fruit and vegetables.

The ratio of total-cholesterol/HDL-cholesterol, not total levels is a determining factor.

9-11 BLOOD LIPID CONCENTRATIONS AND RISK OF MYOCARDIAL INFARCTION

Abnormal lipid concentrations are risk factors for coronary heart disease. The threshold values for lipids are based on population studies from Western countries. Prevention and treatment regimens would exclude most patients with coronary disease in less developed countries who generally have lower lipid concentrations.

This case-control study from Algeria assessed the effect of lipid concentrations on risk of MI, and compared it with 2 case-control studies of similar design done in Western countries

Recruited 67 men in Algeria who had survived a MI, and 70 controls.

Overall, plasma lipid concentrations were systematically lower in Algerians than those recorded in France and Ireland. As in the West, in the Algerian patients with MI, total cholesterol, LDL-cholesterol, and triglycerides

were significantly raised compared with Algerian controls, and HDL-cholesterol was decreased. However the concentrations of these markers rarely rose above the thresholds for intervention recommended in Western countries.

The findings suggest that when cholesterol concentrations are expressed as ratios of total/HDL-c or LDL/HDL-c, the effect of variations in risk of coronary artery disease is more consistent than when values are considered separately. These ratios are therefore good predictors of risk, irrespective of nationality. "We recommend that they be used in the assessment of risk of coronary artery disease worldwide."

Lancet September 29, 2001; 358: 1064-65 Original investigation, first author Sonia Mediene-Benchekor, Universite Es-Senia, Oran, Algeria

	Total-c	LDL-c	HDL-c	Total-c/HDL-c	LDL-c/HDL-c
Algeria					
Patients	197	135	33	6.4	4.3
Controls	175	112	37	5.0	3.3
France					
Patients	222	148	43	5.5	3.7
Controls	226	145	52	4.6	3.0
Ireland					
Patients	240	160	42	6.2	4.1
Controls	234	152	51	5.0	3.3

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Aspirin favored over low-molecular weight heparin

9-12 TINZAPARIN IN ACUTE ISCHEMIC STROKE (TAIST): A Randomized, Aspirin-controlled Trial

The safety and efficacy of heparin in treatment of acute ischemic stroke are not adequately defined.

This trial of the low-molecular-weight heparin tinzaparin (*Innohep*) entered over 1400 patients with acute ischemic stroke within 48 hours of onset. Randomized to: 1) both high-dose and low-dose tinzaparin. and 2) 300 mg aspirin daily. Treatment was continued for 10 days.

Results: At 6 months, no difference in effect between groups on independence, dependence, and death. No difference in effect in any predefined group, including presumed cardioembolic stroke.

Nine in the aspirin group vs none in the tinzaparin group developed symptomatic deep vein thrombosis. Seven in the tinzaparin group developed symptomatic intracerebral hemorrhage vs one in the aspirin group.

"Treatment with tinzaparin within 48 hours of acute ischemic stroke did not improve functional outcome compared with aspirin."

Lancet September 1, 2001; 358: 702-10 Original investigation by the TAIST Investigators, first author Philip M W Bath, University of Nottingham, UK www.thelancet.com

Comment:

This is a good example of a valuable negative study.

Not suitable for primary care

9-13 LONG-TERM WEIGHT LOSS WITH SIBUTRAMINE

"The reluctance of the medical profession to treat obesity is fortunately no longer justified because short-term weight reduction achieved by interventions such as dieting, exercise, and behavior modification programs, can lead to long-term weight loss through the use of effective medicines."

The main objective of pharmacotherapy is to achieve long-term weight loss. There is evidence that even moderate weight loss of 5% to 10% results in reduced morbidity and mortality.

Sibutramine (*Meridia*) enhances satiety primarily by blocking the reuptake of the neurotransmitters, noradrenaline and serotonin. It is postulated that the drug also enhances peripheral noradrenaline function. This leads to increased energy expenditure. Several trials have shown that it is effective in achieving weight loss and maintaining weight loss.

The long-term nature of weight-loss therapy requires a high degree of patient compliance.

This study assessed effectiveness of sibutramine for achieving weight loss.

Conclusion: The drug resulted in sustained and clinically relevant weight loss.

STUDY

1. Randomized, double-blind study followed over 800 private patients (mean age = 43) for 48 weeks. All had a BMI of 30 to 40 kg/m². (Mean = 34) All were otherwise in good health. All had previously unsuccessfully attempted weight loss by dietary measures.
2. Prior to randomization patients were enrolled in a 4-week run-in period with 15 mg of sibutramine daily. Those achieving at least a 2 kg weight loss were then randomized for 44 weeks to:
 - 1) sibutramine 15 mg daily; 2) sibutramine 15 mg intermittently during weeks 1-12, 19-30, and 37-48; or 3) placebo.

RESULTS

1. About 3/4 of subjects completed the trial.
2. Mean weight change

	Weeks 5 to 48	Overall (48 weeks)
Continuous sibutramine	- 3.8 kg (4.0%)	- 7.9 kg
Intermittent sibutramine	- 3.3 kg (93.5%)	- 7.8 kg
Placebo (after 4 weeks drug therapy)	+ 0.2 kg (weight gain)	- 3.8 kg

(Ie, considerable weight loss in the first 4 weeks, the run-in period.)
3. There was a tendency for weight re-gain after the 4-week run-in period in the group assigned to placebo.

4. Abdominal circumference and lipids improved in the sibutramine groups.
5. Blood pressures were stable across all 3 groups. (*See figure 4 p 1336.*) Mean BP at baseline was 132/82. In all 3 groups, BP did not change over 48 weeks. (The investigation entered only normotensive patients.)
6. Adverse effects occurred at similar frequencies across all 3 groups. The proportion was lowest in the intermittent group. 14% experienced adverse events classified as drug related: dry mouth, constipation, increased sweating, and headache. Withdrawals due to adverse events: intermittent = 3.3%; continuous = 6.2%; placebo = 4.5%.

DISCUSSION

1. Patients receiving sibutramine over 48 weeks lost significantly more weight than patients receiving placebo.
2. Even a moderate weight loss of about 5% unquestionably provides benefits. More than 60% of patients in the active groups achieved 5% or more loss compared with 35% of the placebo group.
3. Weight loss reached a maximum at 3 months. Thereafter slowed, but was maintained up to month 12.
4. Patients who do not lose during a first 4 weeks of therapy are not likely to be successful long-term. Long-term treatment should be avoided in this group.
5. Concerning effects on BP, the authors comment that sibutramine gives rise to 2 opposing effects:
 - 1) weight loss results in a decrease;
 - 2) the sympathomimetic effect results in a rise. Generally the effects neutralize each other. (Note these patients were normotensive.)

CONCLUSION

Sibutramine administered for 48 weeks resulted in clinically relevant weight loss compared with placebo. Intermittent dosage was equivalent to continuous administration.

JAMA September 19, 2001; 1331-39 Original investigation, first author Alfred Wirth, Teutoburger-Wald-Klinik, Bad Rothenfelde, Germany www.jama.com

Comment:

Study supported by Knoll. *Meridia* is expensive — the last average wholesale price I accessed was about \$3.00 each 5 mg capsule.

What happens after the first year? What would happen after the drug is discontinued? Can treatment be continued indefinitely? What would be the effects of very-long therapy? RTJ

A possible therapy in addition to diet and weight loss

9-14 METFORMIN IN NON-ALCOHOLIC STEATOHEPATITIS

There is no established treatment for non-alcoholic steatohepatitis except for weight loss in obese patients.

The disease may proceed to fibrosis, cirrhosis, and liver failure. It is associated with hepatic insulin resistance even in the absence of obesity, impaired glucose tolerance, or diabetes.

This preliminary research letter describes 20 patients with non-alcoholic steatohepatitis treated with metformin (*Glucophage*), an agent that improves hepatic insulin sensitivity. All were referred for assessment of liver function because of ultrasonographic evidence of hepatic steatosis (bright liver), and transaminase (**ALT**) elevations. Mean body mass index = 28. Waist circumference was a mean of 98 cm (high). None were alcoholic. Mean fasting blood glucose = 90 mg/dL. None had diabetes as defined by glucose tolerance test.

All patients received nutritional counseling to limit intake of lipids and non-complex carbohydrates.

Metformin (*Glucophage*: 500 mg three times daily) was prescribed to all. Fourteen patients complied. The 6 that did not comply were considered controls.

Body weight and abdominal circumference decreased in both groups. At 4 months, ALT had decreased by 50% in the treatment group. Insulin sensitivity increased. At end of study ALT was normal in 7 study patients vs one control. Liver size decreased by 20% in treatment group vs < 10% in controls.

Metformin was well tolerated as the dose was gradually increased. Lactic acid was normal at baseline. It increased by a mean of 30% in the active treatment group, but was above normal in only one.

Lancet September 15, 2001; 358: 893-94 "Research letter" first author Giulio Marchesini, University of Bologna, Italy. www.thelancet.com

Comment:

Harrison's Principles of Internal Medicine (15th edition) states that non-alcoholic steatohepatitis is the 3rd most common cause of chronic liver disease, after hepatitis C and alcohol. The fatty infiltration may be accompanied by necro-inflammatory activity. Chronic alcoholism is the most common cause of steatohepatitis. It is also associated with type 2 diabetes and lipid disorders.

The patients in this study were moderately obese (BMI = 28; waist circumference = 98 cm. (Normal reference cut point in males = 90 cm.) I believe most US clinicians would advise dietary therapy and weight loss first, and consider metformin only with failure. Take care to be sure kidney function is normal. RTJ

Provocative add-on to physiotherapy

9-15 EFFECT OF LEVODOPA IN COMBINATION WITH PHYSIOTHERAPY ON FUNCTIONAL MOTOR RECOVERY AFTER STROKE

Physiotherapy consists of repetitive exercises aimed at improving motor function. Now, by functional imaging techniques such as PET scanning and MRI, changes induced in the motor cortex can be seen to occur as a result of the exercises. The brain is plastic. It is pliable and capable of being reformed. Specific transmitters are involved. Enhancement of functional motor recovery seems to rely on an increased concentration of norepinephrine at the synapses.

Administering norepinephrine systemically might be dangerous. To increase norepinephrine levels without adverse effects, these investigators administered oral levodopa which is converted to dopamine in the brain. A small percentage of dopamine is converted to norepinephrine.

The study asked: Does levodopa enhance the efficacy of physiotherapy after hemiplegia?

Conclusion: Levodopa enhanced motor recovery.

STUDY

1. Enrolled 53 patients with hemiplegia in a randomized, placebo-controlled, double-blind trial. All had radiologically verified thromboembolic brain infarctions. All strokes had occurred within 3 weeks to 6 months before the start of the study.
2. For the first 3 weeks randomized to: 1) levodopa 100 mg daily by mouth + physiotherapy, or 2) placebo + physiotherapy. For the second 3 weeks they received only physiotherapy to monitor the stability of effects.
3. Assessed motor progress quantitatively by a motor function assessment scale. The goal-oriented approach focused on transfers, control of posture, independent walking, reduction in motor tone, and on increasing range of motion and function of the arms.

RESULTS

1. In the drug intervention group, motor recovery was significantly improved after 3 weeks.
(Motor function improved by 6 points on a 10 point scale compared with 4 points for placebo.)
2. Benefit was independent of initial degree of impairment.
3. The advantage of levodopa was maintained during the following 3 weeks after levodopa was stopped.

DISCUSSION

1. "Our finding that motor recovery is improved by a combination of levodopa and physiotherapy accords with results of other work in animals and clinical trials done with amphetamines."
2. Recovery of motor function was not affected by initial severity of hemiparesis.
3. Several hypotheses may account for the mechanism by which brain plasticity is enhanced. (*See text p 789.*)

CONCLUSION

Levodopa combined with physiotherapy was an effective and safe method for improving motor recovery after stroke. In view of its minimal side effects, it will be a possible add-on during stroke rehabilitation.

Lancet September 8, 2001; 358: 787-90 Original investigation, first author Klaus Scheidtmann, Neurologische Klinik, Bad Aibling, Germany. www.thelancet.com

Comment:

I abstracted this study because it is so provocative. No practical application at this time for primary care. Much more observation and confirmation needed. I will watch for developments with interest. RTJ

C-reactive protein — an excellent prognosticator

9-16 ROLE OF INFLAMMATORY BIOMARKERS IN PREDICTION OF CORONARY HEART DISEASE.

Early atherosclerosis has an inflammatory component characterized by leukocytic infiltration of the vascular endothelial wall. Adhesion and trans-endothelial migration of circulating leukocytes is thought to be important in the initiation and progression of atherosclerotic disease. These processes are mediated largely by cellular-adhesion molecules (CAM) which bind cell to cell.

On histological analysis, human atherosclerotic plaques contain many CAMs. At present, CAMs are not of much value in prediction of vascular disease.

However, a series of large scale prospective studies have consistently shown that the hepatic acute-phase reactant, C-reactive protein, is a strong and independent predictor of future vascular events. Measurement of this inflammatory marker adds to the predictive value of standard lipid screening, particularly in primary prevention. The greater prognostic utility of C-reactive protein reflects the long half-life and stability of the molecule. This is coupled with a lack of circadian variation and low coefficients of variation when measured by high sensitivity assays.

In a larger prospective study of healthy women, C-reactive protein had greater value in predicting relative risk of future cardiovascular events than lipoprotein (a), homocysteine, or LDL-cholesterol. (*Figure page 947.*)

Lancet September 22, 2001; 946-47 "Commentary" by Paul M Ridker, Brigham and Women's Hospital, Boston Mass. www.thelancet.com

A new, more convenient, more effective therapy

9-17 PEGINTERFERON ALFA-2B PLUS RIBAVIRIN COMPARED WITH INTERFERON ALFA-2B PLUS RIBAVIRIN FOR INITIAL TREATMENT OF CHRONIC HEPATITIS C

A sustained virological response (SVR) rate of 40% has been achieved in patients with chronic hepatitis C by a combination of interferon (*Intron A*) and ribavirin (*Rebetol*) given for 24 to 48 weeks.

This trial compared the new preparation PEGinterferon + ribavirin with the old interferon + ribavirin. (PEG denotes polyethylene glycol.) Peginterferon has a longer half life and more favorable pharmacokinetics. This allows more convenient once a week administration.

Conclusion: The combination of peginterferon with ribavirin was more effective in HCV type 1 infection

STUDY

1. Randomized trial entered over 1500 patients with chronic hepatitis C. None had been treated previously. Liver biopsy was consistent with chronic hepatitis in all. All had serum alanine aminotransferase above normal. None had decompensated cirrhosis.
2. Randomized to: 1) peginterferon once weekly intramuscularly + oral ribavirin daily, or 2) interferon three times weekly + oral ribavirin daily for 48 weeks.
3. Primary endpoint — a sustained virological response rate (undetectable hepatitis C virus RNA) at 24 weeks after end of therapy.

RESULTS

1. The SVR rate 24 weeks after end of therapy was significantly higher in the peginterferon + ribavirin group. (54% vs 47%).
2. Among those with type 1 HCV response rates were 42% and 33%.
3. The response rates for genotypes 2 and 3 were about 80% for both groups.
4. Adverse effects were frequent but similar between groups. Dose reductions were necessary in up to 18%. Discontinuation rates were 14% and 13%.

DISCUSSION

1. Patients receiving peginterferon + ribavirin given for 48 weeks achieved a significantly higher SVR rate. The benefit was associated with a decrease in hepatic inflammation.
2. The response rate in the subset of patients with type 1 HCV was substantially improved over those receiving interferon + ribavirin.
3. Response rates in type 2 and 3 were similar and uniformly high with both groups. The benefit of peginterferon in these groups may be one of convenience and ease of administration.

CONCLUSION

The most effective therapy for patients with chronic hepatitis C was peginterferon (a new compound of interferon with polyethylene glycol) once weekly combined with oral ribavirin. The benefit was mainly in patients with HCV type 1 infection.

Lancet September 22, 2001; 958-65 Original investigation, by the International Hepatitis Interventional Therapy Group. first author Michael P Manns, Medical School of Hanover, Germany. www.thelancet.com

Comment:

Robert Reindollar of Charlotte NC was an author-investigator.

What is the responsibility of primary care clinicians regarding chronic hepatitis C? I doubt that many will be willing to be responsible for the prolonged and difficult treatment regimen. Their main responsibility is diagnosis and appropriate referral.

A rare risk. It is preventable

9-18 SEVERE PULMONARY EMBOLISM ASSOCIATED WITH AIR TRAVEL

Air travel is considered a risk factor for pulmonary embolism (**PE**). It has been termed the "economy class syndrome" because of restrictions in passenger movement and the long-time cramped position.

This study investigated relation of duration of travel to risk of PE.

Conclusion: The greater the distance traveled, the higher the risk. Absolute risk was low.

STUDY

1. Systematically reviewed all cases of PE requiring medical treatment on arrival at the busiest airport in France.
2. Obtained data on geographic origins of all flights and the numbers of passengers in order to evaluate the incidence of PE per million passenger-arrivals as a function of distance traveled.
3. PE was suspected if the passenger, within one hour after arrival, experienced chest pain, malaise, syncope, or shortness of breath. Diagnosis was confirmed by ventilation-perfusion scans, angiography, or high resolution CT.

RESULTS

1. In over 135 million passengers arriving from 145 countries, 56 cases of PE occurred. All patients met at least one criterion for PE — syncope, right ventricular dysfunction, shock, tachycardia, and cardiac arrest.
2. Incidence of PE was much higher in passengers traveling more than 3000 miles (1.5 per million passengers) than in those traveling less than 3000 miles (0.01 cases per million).
3. Incidence of PE was 5 cases per million passengers among those traveling more than 6000 miles.
4. Only 5% of patients reported they had left their seats during the flight; 75% reported they were completely immobile during the flight.
5. Almost all patients had high and moderate risk of thromboembolic disease. (Mainly varicose veins, use of estrogens or progestones, age over 40.) Several individuals reported immobilization before the flight, recent surgery and trauma, and previous deep vein thrombosis.
6. In no case did the primary manifestation of PE extend beyond the jetway — all occurred inside the airport.

DISCUSSION

1. PE was related to duration of air travel. Incidence was much higher in those traveling more than 3000 miles or spending more than about 6 hours in flight.
2. The study probably underestimated the incidence of PE because of inability to detect mild cases or incidence beyond the airport. All cases in this report were severe. Several reports have suggested that PE may develop several weeks after air travel.

3. The incidence of deep venous thrombosis (**DVT**) was not studied. It probably is much higher than PE.
4. The sitting position is associated with venous stasis.¹ The double 90 degree angle bends at the knee and hip impede flow. It is also suggested that compression of the lower extremities by the seat may be a risk factor
5. Simple behavioral and mechanical prophylaxis should be considered to prevent air-travel associated PE and DVT. This includes fluids, avoidance of alcohol and smoking, avoidance of restrictive clothing, avoidance of leg crossing. Physical activity such as walking in the aisle and movement of the legs and frequent changes in position while seated should be encouraged. Support stockings may be reasonable advice for those at high risk.

CONCLUSION

Travel in airflights is a significant contributing factor for PE. The greater the distance, the greater the risk.

NEJM September 13, 2001; 345: 779-83 Original investigation, first author Frederic Lapostolle, Service d'Aide Medicale Urgente, Bobigny, France. www.nejm.org

Comment:

1 The sitting position impedes venous return. Lying supine with the legs extended and slightly elevated markedly increases venous return. Sitting post surgery is a risk factor for DVT and PE. Lying supine with the legs slightly elevated reduces risk.

DVT must be much more frequent. Measurement of d-dimer (done within a few minutes) if negative in a patient with low probability of DVT will, with high accuracy, rule out PE and DVT.

Travel other than air must also be a risk factor.

Added to ACE inhibition, spironolactone may retard renal dysfunction

9-19 SPIRONOLACTONE IN ADDITION TO ACE INHIBITION TO REDUCE PROTEINURIA IN PATIENTS WITH CHRONIC RENAL DISEASE

Aldosterone, the sodium-retaining, potassium-excreting hormone, is secreted by the adrenal partly in response to the stimulus of angiotensin II. It has been suggested that aldosterone itself has a role in mediating progressive renal disease

This effect of angiotensin II can be blunted by angiotensin converting enzyme inhibitors (ACE-inhibitors), and by angiotensin II-blockers (which act at the cell surface).

However, suppression of angiotensin secretion by these drugs is not complete.

The drug, spironolactone (*Aldactone*) is a direct aldosterone antagonist. The authors hypothesized that spironolactone would block action of the aldosterone production which remains after ACE inhibition. Thus, spironolactone added to ACE inhibitor might further renal protection.

The study entered eight patients with various renal diseases and persistent proteinuria despite treatment with enalapril (*Vasotec*) for 12 months. Spironolactone 25 mg daily was then added. Protein excretion was measured one month later.

After treatment, there was a mean 54% reduction in protein excretion. There was no significant reduction in BP or creatinine clearance.

"Spironolactone therapy may be useful in patients with proteinuria and renal impairment who still have proteinuria after treatment with ACE inhibitors."

NEJM September 20, 2001; 345: 925-26 Letter to the editor, first author Anastasia Chrysostomou, Royal Melbourne Hospital, Parkville, Australia. **www.nejm.org**

Comment:

The authors comment on another study in which blockade of aldosterone receptors by spironolactone reduced morbidity and death among patients with heart failure who were already receiving ACE inhibitors. It was suggested that the benefits of spironolactone were not due to the hemodynamic effects of spironolactone, but rather on reversing an adverse effect of aldosterone on the myocardium and vascular smooth muscle.

