

# **PRACTICAL POINTERS**

## **FOR PRIMARY CARE**

**ABSTRACTED MONTHLY FROM THE JOURNALS**

**JUNE 2003**

**A 6-DRUG STRATEGY TO REDUCE CARDIOVASCULAR DISEASE BY MORE THAN 80%**

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**AWARENESS ABOUT DEPRESSION**

**ASPIRIN BETTER THAN TICLOPIDINE FOR PREVENTION OF RECURRENT STROKE IN BLACK PATIENTS**

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[www.practicalpointers.org](http://www.practicalpointers.org) [rjames6556@aol.com](mailto:rjames6556@aol.com)

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# HIGHLIGHTS JUNE 2003

## **6-1 A STRATEGY TO REDUCE CARDIOVASCULAR DISEASE BY MORE THAN 80%**

The authors calculate that one third of people taking the pill from age 55 would benefit, gaining on average 11 years of life free from an ischemic heart disease event or stroke.

“The preventive strategy is radical.” It is time to discard the view that risk factors need to be measured and treated individually if found to be ‘abnormal’. Instead, it should be recognized that in Western society the risk factors are high in all of us, so everyone is at risk.”

“There is much to gain and little to lose by the widespread use of these drugs.”

## **6-2 VALUE OF LOW DOSE COMBINATION TREATMENT WITH BLOOD PRESSURE LOWERING DRUGS**

Combining low dose drug treatment for hypertension increases efficacy and reduces adverse effects. Three drugs at half dose are estimated to lower risk of stroke by 63% and ischemic heart disease by 46% at age 60-69.

## **6-3 HEART PROTECTION STUDY OF CHOLESTEROL-LOWERING SIMVASTATIN IN 5963 PEOPLE WITH DIABETES**

Cholesterol-lowering therapy is beneficial for people with diabetes even if they do not already have manifest coronary disease or high cholesterol concentrations. Simvastatin reduced the rate of first major vascular events by about a quarter in a wide range of diabetic patients. Treatment over 5-years could prevent about 5 events per 100 persons treated,

## **6-4 ADHERENCE TO A MEDITERRANEAN DIET AND SURVIVAL IN A GREEK POPULATION**

The traditional Mediterranean diet (**MD**) is characterized by a high intake of vegetables, legumes, fruits, nuts, and cereals (largely unrefined). Also a high intake of olive oil (the principal source of fat), a low intake of saturated fats, and a moderately high intake of fish. Dairy products are mostly in the form of cheese and yogurt. Intake of meat and poultry is low-to-moderate. Wine is often taken with meals.

Greater adherence to the diet was associated with a significant reduction in mortality.

## **6-5 RELATIONSHIP OF WALKING TO MORTALITY AMONG US ADULTS WITH DIABETES**

Regular walking is likely to increase longevity across a diverse spectrum of adults with diabetes. Successful efforts to increase physical activity in the diabetic population could have broad public health benefits.

## **6-6 WALKING, THE BEST MEDICINE FOR DIABETES?**

“Walking is probably the ‘best medicine’ for both prevention and treatment of diabetes mellitus.”

## **6-7 INTENSIVE DIABETES THERAPY AND CAROTID INTIMA-MEDIA THICKNESS IN TYPE 1 DIABETES MELLITUS**

Intensive therapy over an extended time resulting in a mean HbA1c of 7.2% decreased progression of intima-media thickness. Evidence that tight control may delay macro-vascular disease.

## **6-8 NON-ALCOHOLIC FATTY LIVER DISEASE: An Unrecognized Cause Of Cryptogenic Cirrhosis**

Cryptogenic cirrhosis (**CC**) is a significant contributor to liver related morbidity. Non-alcoholic fatty liver disease (**NAFLD**) is the most common cause of CC. The diagnosis of cirrhosis in these patients is usually delayed by almost a decade and is often not established until after the patient develops hepatocellular carcinoma or other complications of advanced liver disease. Once cirrhosis is diagnosed, mortality is greater than that of hepatitis C virus related cirrhosis.

Existing evidence, albeit scant, suggests that NAFLD is a spectrum, progressing from hepatic steatosis to non-alcoholic steatohepatitis, and then on to cirrhosis. Over 6 million US adults have NAFLD, and 640 000 may have cirrhosis. This may exceed the numbers infected with hepatitis C. Prognosis is just as bad.

Diagnosis remains one that is established only after other causes of chronic liver disease have been excluded. NAFLD can be more readily suspected if the patient is obese and has diabetes. Primary care clinicians have an opportunity for prevention by controlling obesity, lipids, and diabetes.

#### **6-9 PROGNOSTIC VALUE OF AMBULATORY BLOOD PRESSURE RECORDINGS IN PATIENTS WITH TREATED HYPERTENSION**

In patients with *treated* hypertension, a higher ABP, systolic or diastolic, predicted cardiovascular events even after adjustment for classic risk factors including office BP. As judged by ABP, office BP may be misleading.

#### **6-10 AMBULATORY BLOOD-PRESSURE MONITORING IN CLINICAL PRACTICE**

24-hour ABP monitoring yields readings during all the patient's activities, and gives a far better representation of the "blood pressure burden" than that obtained during office visits.

ABP should be used more often in clinical practice.

"For those whose ambulatory blood pressure is truly normal (< 130/80) despite an elevated office blood pressure, and in whom there is no evidence of other cardiovascular risk factors or target-organ disease, avoidance of unnecessary drug therapy would be a clear benefit of the monitoring procedure."

#### **6-11 USE OF ANTIOXIDANT VITAMINS FOR THE PREVENTION OF CARDIOVASCULAR DISEASE**

A lack of beneficial effect was seen consistently for various doses of these two vitamins in diverse populations. The routine use of vitamin E is not supported. The use of beta carotene is associated with a small but significant excess of all-cause mortality and cardiovascular death.

#### **6-12 EFFECTIVENESS OF NEURAMINIDASE INHIBITORS IN TREATMENT AND PREVENTION OF INFLUENZA A AND B**

Evidence consistently supports the view that zanamivir (*Relenza*) and oseltamivir (*Tamiflu*) are clinically effective in treating and preventing flu. Evidence is limited for treatment of certain populations as well as for prevention strategies. The numbers needed to treat to prevent one person from developing flu may be high.

Choosing individuals for whom the drugs are indicated would be a clinical-judgment call, depending largely on cost, personal preference, and likelihood of severe complications from flu.

The drugs are no substitute for vaccination. They may be adjunctive therapy on occasion.

#### **6-13 REGRESSION OF MICROALBUMINURIA IN TYPE 1 DIABETES.**

Urinary albumin excretion does not imply inexorable progression of diabetic nephropathy. Regression frequently occurs, associated with lower HbA1c levels, lower BP, and lower levels of cholesterol and triglycerides.

#### **6-14 NONINVASIVE DETECTION OF CLINICALLY OCCULT LYMPH-NODE METASTASES IN PROSTATE CANCER.**

High resolution MRI with magnetic iron-containing nanoparticles allowed detection of small and otherwise undetectable lymph-node in patients with metastatic PC.

#### **6-15 LEISURE ACTIVITIES AND THE RISK OF DEMENTIA IN THE ELDERLY**

Participation in leisure-time mental activities was associated with reduced risk of dementia and rate of decline in memory.

Frequent participation in leisure-cognitive activities was associated with a reduced risk of dementia over an ensuing 5 years. The activities include playing board games, reading, playing musical instruments, and doing crossword puzzles. The brain has use-dependent plasticity. Effortful mental activity may not only strengthen existing connections, but stimulate neurogenesis. Persistent engagement by the elderly in effortful mental activities may promote plastic changes in the brain that circumvent the pathology underlying the dementia.

## 6-16 AWARENESS ABOUT DEPRESSION: Important for All Physicians

A nationally representative household survey of the 48 contiguous United States found that the lifetime prevalence of major depression is 16%. Recognition and treatment of depression in primary care practice is woefully inadequate. Screening is indicated in primary care practice. A helpful website is cited.

## 6-17 ASPIRIN AND TICLOPIDINE FOR PREVENTION OF RECURRENT STROKE IN BLACK PATIENTS: A Randomized Trial

Ticlopidine was *not* more effective than aspirin in preventing recurrent stroke in Afro-Americans. Aspirin is a better treatment than ticlopidine for aspirin-tolerant Afro-Americans with noncardioembolic ischemic stroke.

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## What? A Pill For Everyone Over Age 55? Outrageous? Or The Brave New World?

### 6-1 A STRATEGY TO REDUCE CARDIOVASCULAR DISEASE BY MORE THAN 80%

“Heart attacks, stroke, and other preventable cardiovascular diseases (CVD) kill or seriously affect half the population of Britain.”

Drugs which lower 3 risk factors—LDL-cholesterol, BP, and platelet adhesiveness (with aspirin) reduce incidence of ischemic heart disease and stroke. Reducing homocysteine levels with folic acid may also lower risk.

The authors describe a strategy to prevent CVD based on these principles; a daily pill containing 6 components, each lowering one of the four factors. “The pill would be suitable for people with cardiovascular disease and for everyone over a specified age (say 55).”

Conclusion: The pill could largely prevent heart attacks and stroke.

## STUDY

1. Quantified efficacy and adverse effects of the proposed formulation from published meta-analyses of randomized trials and cohort studies.
2. A proposed pill could contain:

	Standard dose
Simvastatin 40 mg	40 mg
Hydrochlorothiazide or chlorthalidone 12.5 mg	25 mg
Atenolol 25 mg	50 mg
Enalapril 5 mg	10 mg
Folic acid 800 micrograms	RDA = 400 micrograms
Aspirin 75 mg.	Low dose

(All are generic except simvastatin. Simvastatin may shortly go off patent.)
3. Calculated the combined effect of the drugs in changing the 4 risk factors.
4. Calculated the years of life gained without a heart attack or stroke if persons without a previous cardiovascular event used the pill from age 55.

## RESULTS

1. The pill could reduce LDL-c by 1.8 mmol/L (70 mg/dL); BP by 11 mg diastolic; serum homocysteine by 3 micromoles/L. The effect of aspirin was estimated to be a 34% lowering in risk. Thus, the authors argue, if 100 persons were treated, statins would prevent ischemic heart disease events in 61, leaving 39; 46% of the 39 would be prevented by BP lowering, leaving 21; 16% of these would be prevented with folic acid, leaving 18; and 34% of these would be prevented by aspirin, leaving 12. Thus, 88% of events would have been prevented.
2. The authors calculate that one third of people taking the pill from age 55 would benefit, gaining on average 11 years of life free from an ischemic heart disease event or stroke.
3. Adverse effects: The pill would cause symptoms in about 15% of people, depending on the precise formulation. Aspirin would cause the most serious adverse effects, mainly due to hemorrhage. However, although aspirin increases risk of hemorrhagic stroke, the benefit in reducing thrombotic stroke outweighs the risk.
4. Adverse effects: The pill may not be suitable for some people. Beta-blockers are unsatisfactory for people with asthma. Some are intolerant to aspirin. Monitoring to prevent rare serious adverse effects might be considered—serum creatine kinase and transaminase (for rhabdomyolysis and hepatitis caused by statins), and serum potassium and creatinine (for acute renal failure caused by ACE). “However, the values of such monitoring are uncertain.”

## DISCUSSION

1. The Polypill strategy, based on a single daily pill containing 6 components as specified, would prevent 88% of heart attacks and 80% of strokes. “About 1 in 3 people would directly benefit, each on average gaining 11-12 years without a heart attack or stroke (20 years in those age 55-64)”
2. “We are confident that the estimated effect is accurate.”
3. Other than the statin (in respect to its benefit on ischemic heart disease) omitting a single component would have a relatively minor impact on the combined effect of the residual components.
4. Each component has been used in medical practice for more than 10 years with substantial evidence of safety and efficacy.
5. Who should take the pill? Patients with established cardiovascular disease (secondary prevention). Patients with diabetes (primary prevention). Among patients without existing disease, about 95% of deaths from ischemic heart disease and stroke occur in people over age 55. Treating *everyone* in this age group would prevent nearly all such deaths. “Using different age cut-offs for men and women, or smokers and non-smokers or combining several risk factor values with age and sex to produce individual estimates of overall risk would *add little* discrimination and would probably not justify the added complexity and cost.”
6. “The best approach is therefore to treat people with known occlusive vascular disease and everyone aged 55 and over. There is no need to measure the four risk factors before starting treatment, because intervention is effective whatever the initial levels of the risk factors, nor to monitor the effect of the treatment . . . ”

## CONCLUSIONS

“The preventive strategy is radical.” It is time to discard the view that risk factors need to be measured and treated individually if found to be ‘abnormal’. Instead, it should be recognized that in Western society the risk factors are high in all of us, so everyone is at risk.”

“There is much to gain and little to lose by the widespread use of these drugs.”

BMJ June 28, 2003; 326: 1419-23 Original investigation by N J Wald and M R Law, Wolfson Institute of Preventive Medicine, London University, UK [www.bmj.com/cgi/content/full/7404/1419](http://www.bmj.com/cgi/content/full/7404/1419)

Comment:

I first thought the authors were presenting the “pill” tongue in cheek. Not so. They are serious. Indeed, they have filed a patent application on the formulation.

Come to think of it, many persons in the USA are already taking one, two, three, or four of the components. Why not combine them?

The theory is based on a reasonable belief that reductions in BP, cholesterol, platelet adhesiveness, and homocysteine would benefit regardless of their initial levels (even if the initial levels are considered within “normal” limits.)

Is it ethical for physicians to recommend drugs for prevention by persons in whom the risk is not established? At present millions take low dose aspirin, folic acid, vitamin D and calcium in anticipation of a perceived risk, and in whom the risk is not established. Millions more take “dietary supplements” without defined reason or indication. And with uncertain benefits.

Still, there seems to be something wrong about recommending drugs which have known and unknown adverse effects, for *everyone*. This goes a big step beyond classical medical treatments. Could this be the way medicine is headed?

Legal problems? I suspect so. However, if widespread use of drugs in patients without established risk or without even testing for risk factors, becomes the standard of care, legal liability will lessen.

Adverse effects, and even death are bound to occur if use is universal. Much more clinical investigation is required. I cannot imagine the FDA approving such usage. RTJ

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## 6-2 VALUE OF LOW DOSE COMBINATION TREATMENT WITH BLOOD PRESSURE LOWERING DRUGS

Lowering systolic BP by 10 mm Hg or diastolic by 5 mm Hg reduces risk of stroke by about 35%, and ischemic heart disease by about 25% at age 65. This applies across all levels of BP in Western society, not only in “hypertension”.

BP-lowering drugs should be more widely used. Which drugs are most appropriate? Are combinations of drugs safer and more effective than single drugs? Are lower doses of drugs in combination a better approach than high doses of single drugs? This systematic review provided answers.

Conclusion: Combinations of low doses increase efficacy and decrease adverse effects.

## STUDY

1. Meta-analysis of over 300 randomized, double-blind, placebo-controlled trials considered 5

drug classes: thiazide diuretics, beta-blockers, ACE inhibitors, angiotensin II blockers, and calcium channel blockers at a fixed dose. Fifty trials tested the effect of two drugs separately and in combination.

Reference pharmacopeias defined the “usual dose”.

2. About 10 000 subjects received the drugs; over 16 000 received placebo.
3. Examined the effect of dose and combination treatment on efficacy and adverse effects.
4. Most subjects had high BP (typically 90-110 mm Hg diastolic). Some studies provided evidence of efficacy at lower BP.
5. Efficacy defined as reduction in both systolic and diastolic for a specified dose, expressed as the change in the treated group minus that of the placebo group.
6. . Determined whether the combined effect of two drugs of different categories was additive with respect to BP and adverse effects.
7. Main outcomes = placebo-adjusted reductions in BP and prevalence of adverse effects.

## RESULTS

1. All five categories of drugs produced similar reductions in BP (average 9/6 mm Hg) at standard dose, and 7/4 at half dose.
2. Effect of lowering BP was greater in patients with higher BP.
3. The BP-lowering effects of different categories of drugs were additive.
4. Efficacy of BP lowering in drugs used at half dose separately or in combination:

	One drug	Two drugs	Three drugs
Systolic BP reduction (mm HG)	7	13	20
Diastolic	4	7	11

5. Adverse effects ( % of people with one or more symptoms attributable to treatment):

	Half dose	Standard dose	Twice standard dose.
Thiazides	2	10	18
Beta-blockers	6	8	9
ACE inhibitors	4	4	4
Angiotensin II	-2	0	2
Calcium blockers	2	8	15

(Symptoms attributable to thiazides, beta-blockers, and calcium blockers were strongly dose related.

ACE inhibitor related symptoms (mainly cough) were not dose related. Angiotensin II blockers caused no excess of symptoms.)

6. Prevalence of symptoms with 2 drugs in combination was less than additive. Single drugs caused symptoms in 5%; two drugs together caused symptoms in 7.5%
7. Adverse metabolic effects (changes in cholesterol and potassium) were negligible at half dose.

## DISCUSSION

1. All drugs produced similar reductions on BP and were effective from all baseline treatment levels.

2. Use of BP-lowering drugs should be determined by a person's overall risk rather than the BP alone.
3. Adverse effects on drugs used at half dose were much less common. Efficacy of drugs used in combination was additive in lowering BP, but less than additive in producing adverse effects. "Combination of two or three drugs used at half dose is preferable to one or two drugs used at standard dose."
4. One drug at half dose is estimated to reduce risk of stroke by 29%; two drugs at half dose-49%; and three drugs at half dose – 63%. And incidence of ischemic heart disease by 19%; 34%; and 46%.

## CONCLUSION

Combining low dose drug treatment for hypertension increases efficacy and reduces adverse effects. Three drugs at half dose are estimated to lower risk of stroke by 63% and ischemic heart disease by 46% at age 60-69.

BMJ June 28, 2003; 326: 1427-31 Original investigation, first author M R Law, Wolfson Institute of Preventive Medicine, University of London [www.bmj.com/cgi/content/full/7404/1427](http://www.bmj.com/cgi/content/full/7404/1427)

### Comment:

I believe the standard drug treatment of hypertension is headed this way. Most patients require two drugs or more to reach target levels. Why not combine three in low doses? RTJ

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## *Should All Patients With Diabetes Take Statin Drugs?*

### **6-3 HEART PROTECTION STUDY OF CHOLESTEROL-LOWERING SIMVASTATIN IN 5963 PEOPLE WITH DIABETES**

Individuals with diabetes are at increased risk of cardiovascular disease (CVD) morbidity and mortality even though typically the plasma LDL-cholesterol levels of persons with diabetes are similar to the general population. Perhaps, as a consequence, most people with diabetes do not receive cholesterol-lowering drugs despite their high risk of cardiovascular events.

Observational studies indicate a continuous positive relationship between CVD and LDL-cholesterol levels, without any definite threshold below which a lower concentration is *not* associated with lower risk. The relationship is approximately linear when plotted on a doubling scale.<sup>1</sup> The absolute risk of coronary mortality at each level of blood cholesterol is 3 to 5 times higher in the presence of diabetes.

This study asked whether lowering LDL-cholesterol might be worthwhile among people with diabetes who do not already have symptomatic coronary disease, and regardless of their baseline LDL-c levels.

Conclusion: Cholesterol-lowering was beneficial for people with diabetes even when they did not have "high" levels of cholesterol.

## STUDY

1. Entered over 5900 UK adults (mean age = 62) with diabetes. Baseline LDL-cholesterol = 123 mg/dL.
2. Entered an additional 14 500 patients with occlusive vascular disease (but no diagnosis of diabetes).

Baseline LDL-cholesterol = 130 mg/dL

3. Randomized to: 1) the statin drug simvastatin (*Zocor*) 40 mg daily, or 2) placebo.
4. Major endpoints were the first major coronary event--non-fatal or fatal myocardial infarction, or coronary death.
5. Follow-up = 5 years. Comparisons were made on an intention-to-treat basis.

## RESULTS

1. Simvastatin reduced LDL-c by about 39 mg/dL during the 5-years. 2. In both groups, highly significant reductions occurred in the first-event rate for major coronary events, for stroke, and for revascularizations.

A. Diabetes:	Simvastatin (%)	Placebo (%)	Absolute difference	NNT*
Major coronary events	9.4	12.6	3.2	31
Strokes	5.0	6.5	1.5	66
Revascularizations	8.7	10.4	1.7	58
Major vascular events	20.2	25.1	4.9	21
B. No diabetes				
Major coronary events	8.5	11.5	2.0	50
Strokes	4.0	5.4	1.4	71
Revascularizations	9.3	12.3	3.0	33
Major vascular events	19.6	25.2	5.6	18

(\* *The number of patients needed to be treated over 5 years to benefit one.*)

3. Simvastatin provided highly significant benefits, with reductions, compared with placebo, of about one quarter in adverse outcomes.
4. About half of the patients with diabetes did *not* have a diagnosis of arterial disease at entry. In this group, simvastatin also provided highly significant benefits.<sup>2</sup> Risks were reduced from 32.9% in the placebo group to 25.6% in the treated group. (Absolute difference = 7.3%; NNT = 14)
5. There was a 27% reduction in events among diabetic patients who had an entry LDL-c less than 3.0 mmol/L (116 mg/dL).
6. There was a reduction in risk among subgroups of diabetic patients: age over 65, varying duration of diabetes, type or control of diabetes, and those with total-c below 193 mg/dL,
7. Reductions in risk also were highly significant among those without diabetes.

## DISCUSSION

1. Benefits of simvastatin were evident for diabetic patients irrespective of existing arterial disease or presenting lipid concentrations. Benefits from simvastatin were similar in patients without diabetes who had established vascular disease.
2. Continued treatment with simvastatin reduced the rate of not just the first occurrence of events, but also subsequent events.

3. Blood pressure control, aspirin, beta-blockers, and ACE inhibitors could add to the protective effects of lipid control in diabetic patients.
4. “Decisions about whether to initiate statin therapy should now be guided by an individual’s estimated risk of having either a heart attack or stroke, or needing some other revascularization procedure.” In these patients statins should be considered irrespective of their initial cholesterol concentrations.
5. The investigators estimate that lipid-lowering over 5-years in patients with diabetes who do not have occlusive arterial disease would prevent 45 people per 1000 treated from having a major event. It would also reduce risk of subsequent events.

## CONCLUSION

Cholesterol-lowering therapy was beneficial for people with diabetes even if they did not already have manifest coronary disease or high cholesterol concentrations. Simvastatin reduced the rate of first major vascular events by about a quarter in a wide range of diabetic patients. Treatment over 5-years could prevent about 5 events per 100 persons treated,

Lancet June 14, 2003; 361: 2005-16 Original investigation by the Heart Protection Study Collaborative Group, Radcliffe Infirmary, Oxford, UK [www.thelancet.com](http://www.thelancet.com)

Comment:

### 1 My understanding of the “doubling scale”:

For risk factors such as systolic BP, LDL-cholesterol, fasting plasma glucose, any increase will increase risk of complications; and any decrease will decrease risk of complications (down to a certain level which is usually not clearly defined, but is well below the range commonly seen in Western populations.)

Thus, starting at a high systolic BP, lowering it by a factor of X will reduce risk by half. Lowering it again by a factor of X will reduce risk by a half from the previous level of risk. And so on.

Conversely, increasing a baseline low systolic BP by a factor of X will increase risk by a factor of 2; increasing it again by a factor of X will increase risk by twice the previous risk. And so on.

As systolic rises, risk in absolute terms doubles for each rise of X. The increase in absolute terms is very low when systolic rises from its lowest level to the next lowest. As each higher level is reached, risk rises in an exponential (doubling) manner. You would get much more “bang for the buck” by treatment which lowers a very high LDL to a moderately “high” LDL, than you would get by lowering LDL from a moderately high level to “normal” and below.

Consider various LDL baseline levels and the change due to statin drug:

Baseline LDL	Treatment LDL
180	160
160	140
140	120
120	100
100	80
80	60

Each step will lower risk, but the absolute benefit from each step decreases as the baseline LDL decreases.

### 2 Should all patients with diabetes take a statin drug? RTJ

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## Why Some Greeks Live Longer.

### 6-4 ADHERENCE TO A MEDITERRANEAN DIET AND SURVIVAL IN A GREEK POPULATION

The traditional Mediterranean diet (MD) is characterized by a high intake of vegetables, legumes, fruits, nuts, and cereals (largely unrefined). Also a high intake of olive oil (the principal source of fat), a low intake of saturated fats, and a moderately high intake of fish. Dairy products are mostly in the form of cheese and yogurt. Intake of meat and poultry is low-to-moderate. Wine is often taken with meals.

This study assessed the relation between adherence to the MD and mortality.

Conclusion: Greater adherence was associated with a significant reduction in mortality.

#### STUDY

1. Population-based, prospective investigation involved over 22 0000 adults in Greece. (Over 81 000 person-years) All completed an extensive, validated food-frequency questionnaire at baseline.
2. Adherence to the diet was judged by a 10-point scale: divided scores into groups--0 to 3; 4-5; 6-9. (Ten being the highest.) The highest intake-group had a substantial increase in intake of mono-unsaturated fats, and a substantial reduction in intake of meat.
3. Assessed relation between the diet and total mortality, and mortality due to coronary disease and cancer.
4. Follow-up = a median of 44 months.

#### RESULTS

1. Over follow-up there were 275 deaths.
2. A higher degree of adherence to the MD was associated with a reduction in mortality

Hazard ratios\* of death associated with a two-point increment in score:

Total mortality	0.75
Death due to coronary heart disease	0.67
Death due to cancer	0.76

(\* A hazard ratio of 0.75 indicated that death was less likely as compliance with the MD increased.

Compared with 100 deaths in persons who were not compliant, 75 deaths occurred in the more compliant groups for each step up in compliance.)

3. Associations between individual food groups comprising the MD and total mortality were generally not significant. (*Apparently, the benefit depends on general adherence to the diet. RTJ*)
4. Benefit was evident irrespective of sex, smoking status, level of education, body-mass index, and physical activity.
5. Relation between mortality and the diet score was significant among participants over age 55, but not among those younger

#### DISCUSSION

1. A high adherence to the traditional MD was associated with a reduction in total mortality. A 2-point

increment in the score corresponded to a 25% reduction in total mortality. Reduction in mortality was evident with respect to both death from coronary heart disease and cancer.

2. However, strong associations with mortality were *not* evident for each of the components of the diet. Individual components may have small effects that emerge only when the components are integrated into a simple, unidimensional score.
3. The association between greater adherence to the MD and reduced mortality became stronger with increasing age. This might reflect increasing cumulative exposure to the diet.
4. These results are compatible with two randomized trials of secondary prevention of coronary heart disease through use of variants of the MD.

## CONCLUSION

Greater adherence to the traditional MD was associated with significant reductions in mortality.

NEJM June 26, 2003; 348: 2599-2608 Original investigation, first author Antonia Trichopoulou, University of Athens Medical School, Greece. [www.nejm.org](http://www.nejm.org)

An editorial in this issue by Frank B Hu, Harvard School of Public Health, Boston MA comments:

See Lancet 1994; 343: 1454-59 for a secondary prevention study. "Mediterranean Alpha-Linolenic Acid-Rich Diet In Secondary Prevention Of Coronary Heart Disease." The alpha-linolenic acid mimics the n-3 content of the traditional diet in Crete. In patients with prior myocardial infarction, coronary events were reduced by 73% over 2 years, total mortality was reduced by 70%.

Also Lancet 2002; 360: 1455-61 for another secondary prevention study: "Effect Of An Indo-Mediterranean Diet On Progression Of Coronary Artery Disease In High-Risk Patients" The diet was associated with a reduction in fatal myocardial infarction by one third and rate of sudden death by two thirds.

Small amounts of alcohol (wine), cereal fiber (unprocessed grains), and foods with a low glycemic load are beneficial. Trans fatty acids should be avoided. Canola oil (rapeseed) also contains mono-unsaturated fatty acids and is a good source of the n-3 alpha linolenic acid.

*(Note the diet has been reported to benefit patients who have established coronary heart disease (secondary prevention), as well as those who do not (primary prevention).*

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## 6-5 RELATIONSHIP OF WALKING TO MORTALITY AMONG US ADULTS WITH DIABETES

Walking is associated with a reduced incidence of diabetes (**DM**). Walking and other forms of exercise have been reported to be key components of lifestyle changes which prevent progression to DM among people with impaired glucose tolerance. Among those with DM, physical activity improves insulin sensitivity, glycemic control, and cardiovascular disease (**CVD**) risk factors.

This study assessed whether walking reduces mortality among patients who already have diabetes.

Conclusion: Walking was associated with lower mortality.

## STUDY

1. In 1990-91 a prospective cohort study entered a representative sample of over 2800 adults in the US who had DM.
2. Assessed physical activity by interview asking how often participants walked during the previous 2 weeks and the average number of minutes they spent walking each time.
3. Followed for 8 years. Main outcome measure = all-cause and CVD mortality. Compared mortality according to amount of walking reported. The study controlled for sex, age, body mass index, smoking and comorbid conditions

## RESULTS

1. About one half reported not walking at all, ¼ reported walking 0 to 1.9 hours per week, ¼ walked over 2 hours per week.
2. Compared with inactive individuals, those who walked at least 2 hours per week had a lower all-cause mortality (2.8% vs 4.4% per year) and a lower CVD mortality (1.4% vs 2.1% per year). (In absolute terms, 1.6% and 0.7% difference. NNT = 62 and 142)
3. Mortality rates were lowest for persons who walked 3 to 4 hours/wk. And for those who reported that their walking involved *moderate* increase in heart and breathing rates.
4. The protective association of physical activity was observed for persons of varying sex, age, race, body mass index, diabetes duration, comorbid conditions, and physical limitations.

## DISCUSSION

1. In this nationally representative sample of Americans with diabetes, higher levels of walking and total leisure time activity were associated with significant reductions in all-cause mortality over 8 years.
2. Walking at least 2 hours per week was associated with about a 33% reduction in all-cause and CVD mortality. Walking up to 4 hours per week was associated with a 54% reduction in mortality.
3. Walking at moderate intensity (“brisk”) levels was associated with the greatest reduction in mortality rates.
4. “Brisk walking on a regular basis is a key health behavior for persons with diabetes.” The lowest mortality was in the group reporting moderate increase in perceived heart and breathing rates, but not in those with large perceived increases. (Symptoms in the latter group may be due to underlying cardiovascular or lung disease—a confounding effect.)
5. Benefits of walking on longevity extended across diverse characteristics including age, sex, race, BMI, time since diabetes diagnoses, and presence of comorbidity and functional limitations.
6. Physical activity is associated with an increase in HDL-cholesterol, decreased BP, decreased insulin levels, weight loss, decreased LDL-cholesterol, improved insulin sensitivity and glycemic control.
7. Exercise may forestall functional decline.
8. The authors estimate that one death per year may be preventable for every 61 people who walk at least 2 hours per week.

## CONCLUSION

Regular walking is likely to increase longevity across a diverse spectrum of adults with diabetes. Successful efforts to increase physical activity in the diabetic population could have broad public health benefits.

Archives Internal Medicine June 23, 2003; 163: 1440-1447 Original investigation, first author Edward W Gregg, Centers for Disease Control and Prevention, Atlanta GA. [www.archinternmed.com](http://www.archinternmed.com)

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### **6-6 WALKING, THE BEST MEDICINE FOR DIABETES?**

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

“Type 2 diabetes (**DM**) has become a pandemic.” The excess risk of fatal coronary heart disease (**CHD**) for those with clinical diabetes over 10 to 15 years is similar to that conferred by a prior CHD. The combination of a long-duration diabetes associated with a preexisting CHD is associated with a particularly high risk of fatal CHD and total mortality.

Physical inactivity is a major cause of DM. Increased physical activity is associated with substantial reductions in risk. Regular walking or other moderate exercise in conjunction with dietary changes can prevent development of type 2 DM in the majority of persons with impaired glucose tolerance. Lifestyle modifications are far more effective than metformin therapy. Exercise itself, without diet, can result in reductions in HbA1c.

Although the evidence of overall benefits of walking is overwhelming, the shape of the dose-response relationship and the effects of exercise intensity are not entirely consistent. Various studies have reported different threshold effects—a higher or lower walking time of walking and the degree of effort. The Institute of Medicine has raised their recommendation to 60 minutes per day of moderate physical activity.

“Walking is probably the ‘best medicine’ for both prevention and treatment of diabetes mellitus.”

Archives Internal Medicine June 23, 2003; 163: 1397-98 Editorial by Frank B Hu, Harvard School of Public Health, Boston Mass. [www.archinternmed.com](http://www.archinternmed.com)

Comment

Walking may prevent development of DM in patients with impaired glucose intolerance, may lessen severity in DM in those with the disease, and may prevent cardiovascular complications of DM

Walking clubs for patients with diabetes were formed over 50 years ago. I doubt if success in motivating walking is any better now than it was at that time. RTJ

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### ***Tight Control Delayed Macro-Vascular Disease***

### **6-7 INTENSIVE DIABETES THERAPY AND CAROTID INTIMA-MEDIA THICKNESS IN TYPE 1 DIABETES MELLITUS**

The relative risk of cardiovascular disease (**CVD**) in patients with type 1 diabetes (**DM-1**), compared with non-diabetic persons, may be increased by a factor of 10. Morbidity and mortality from CVD in these patients is high. Whether chronic hyperglycemia contributes to risk is not known.

This study examined the relation of glycemic control to progression of carotid intima-media thickness (a measure of atherosclerosis) in a population of patients with DM-1.

Conclusion: Intensive therapy resulted in decreased progression of intima-media thickness.

## STUDY

### 1. The DCCT trial:

A. During the Diabetes Control and Complications Trial (**DCCT**) over 1400 patients with DM-1 were randomized to 1) intensive diabetes therapy, maintaining a mean HbA1c of 7.2%, or 2) standard therapy maintaining a mean HbA1c of 9% over a follow-up of 6.5 years.

B. Intensive therapy reduced progression of *micro*-vascular complications by 35% to 76%.

### 2. The EDIC trial:

A. After completion of the DCCT, patients (over 1200 remaining) entered the Epidemiology of Diabetes Interventions and Complications Study (**EDIC**). Half of the subjects were from the intensively treated group; half from the standard therapy group.

B. The EDIC study used B-mode ultrasonography to measure thickness of the intima-media (**I-M**) wall of the carotid artery. (The thickness of this wall is a well-established index of atherosclerosis. It correlates with prevalent and incident coronary atherosclerosis and stroke.)

C. Carotid ultrasonography was repeated at 1 to 2 years into the EDIC study (about 8 years after the DCCT study) and again about 4 years later. Healthy age and sex-matched controls were recruited to serve as contemporaneous controls in whom I-M-thickness was determined.

D. Analyzed changes in the I-M thickness over time along with associated risk factors.

## RESULTS

1. In the EDIC trial, the mean progression of the I-M thickness was significantly *less* in the DCCT group that had received intensive therapy during the DCCT than in the group that received conventional therapy.

(Progression 0.032 mm vs 0.046 mm.)

2. Progression of I-M thickness was also associated with age, systolic BP, smoking, ratio of LDL to HDL cholesterol, urinary albumin excretion rate, as well as mean HbA1c.

## DISCUSSION

1. This study assessed the long-term effect of intensive treatment of type 1 DM (presumably mediated through improved glycemic control) on the thickness of the carotid wall over time.

2. “Our results demonstrate an association between glycemia and intima-media thickness, a sensitive marker of coronary and cerebral vascular disease in patient with type 1 diabetes.”

3. As reported by others, these investigators also found the conventional cardiovascular risk factors to be related to the I-M thickness.

## CONCLUSION

Intensive therapy over an extended time resulting in a mean HbA1c of 7.2% decreased progression of intima-media thickness. Evidence that tight control may delay macro-vascular disease.

NEJM June 5, 2003; 348: 2294-303 Original investigation, by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Intervention and Complications (DCCT/EDIC Research Group), Bethesda MD  
www.nejm.org

### Comment:

I believe it would not be difficult for primary care clinicians to extrapolate the results from these two studies to patients with type 2 DM.

All risk factors which lead to complications of CVD in patients with DM need strict control. Hyperglycemia is likely another risk factor for *macro*-vascular disease. RTJ

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## 6-8 NON-ALCOHOLIC FATTY LIVER DISEASE: An Unrecognized Cause Of Cryptogenic Cirrhosis

“Grand Rounds” at Johns Hopkins presents a case of non-alcoholic fatty liver disease (NAFLD), a cause of cryptogenic cirrhosis (CC). CC is a common cause of liver-related morbidity and mortality in the USA. NAFLD is the most common cause of CC.

The patient was a 53-year old man referred because of intractable right pleural effusion, progressive fatigue, and exertional dyspnea. He had no history of heart disease or hypertension. He had been obese since high school and had diabetes diagnosed 2 years ago.

ECG and echocardiogram were normal. Imaging studies demonstrated splenomegaly, ascites, intra-abdominal varices, but no lung masses or cardiomegaly. Aminotransferases and alkaline phosphatase were only slightly raised; serum albumin 3.3 g/L, INR 1.4, platelet count low at  $78 \times 10^3$ /uL.

A presumptive diagnosis of portal hypertension prompted a more extensive investigation for risk factors of chronic liver disease: He had never received transfusions, denied injecting drugs, had no exposure to toxins. He had drunk one glass of wine daily<sup>1</sup> for the past 3 years for cardio-protection. There was no family history of liver disease. Tests for viral hepatitis, autoimmune liver disease, iron overload, and alpha-1 antitrypsin were negative. Hepatic venous pressure measurements were consistent with portal hypertension. Liver biopsy demonstrated cirrhosis.

He was treated with repeated thorocenteses, fluid restriction, low sodium diet and paracentesis with albumin supplementation. A transjugular intrahepatic shunt was performed. Patient is awaiting liver transplant.

### *Nonalcoholic fatty liver disease:*

NAFLD develops in patients who are not heavy drinkers. Pathological features are similar to alcohol induced liver damage, a spectrum ranging from simple hepatic steatosis (fatty liver) to steatohepatitis to cirrhosis. Non-alcoholic steatohepatitis is believed to be an intermediate stage of liver damage. It is characterized by hepatic steatosis plus liver cell injury, inflammation, and death. A fibrogenic response occurs, gradually progressing to bridging fibrosis and cirrhosis.

Currently there are no non-invasive tests to diagnose or stage NAFLD. Liver biopsy remains the most sensitive test, but cannot distinguish NAFLD from other causes of fatty liver disease, such as alcohol abuse. The degree of liver enzyme elevation does not correlate with the level of damage seen histologically.

Diagnosis remains one that is established only after other causes of chronic liver disease have been excluded. NAFLD can be more readily suspected if the patient is obese and has diabetes.

#### *Causes Of Cryptogenic Cirrhosis:*

CC cannot be explained by chronic viral hepatitis, alcohol abuse, toxin exposure, autoimmune disease, congenital causes of chronic liver disease, vascular outflow obstruction, or biliary tract disease.

Emerging evidence suggests that NAFLD is the most common cause of CC. (First suggested in 1999<sup>2</sup>)

Patients with NAFLD are about one decade older, but otherwise are similar to patients with non-alcoholic steatohepatitis. Both groups have a high prevalence of obesity and diabetes.

#### *Diagnostic imaging tests:*

Have limited utility in diagnosing NAFLD. They cannot be routinely recommended. None of the tests are able to detect inflammation or fibrosis. Steatosis may diminish and disappear as fibrosis and cirrhosis develop.

Imaging studies (ultrasound, CAT scan, MRI) are useful in demonstrating steatosis, in early stages when fat accumulation is moderate to severe. By the time cirrhosis develops, fat may not be excessive in the liver. A diagnosis of cirrhosis can be inferred only when signs of portal hypertension develop (splenomegaly, ascites, varices).

#### *Clinical implications of NAFLD-related cirrhosis:*

Existing evidence, albeit scant, suggests that non-alcoholic steatohepatitis progresses to cirrhosis at a rate similar to other causes of chronic hepatitis. Over 6 million US adults have NAFLD, and 640 000 may have cirrhosis. This may exceed the numbers infected with hepatitis C. Prognosis is just as poor. .

#### *Treatments for NAFLD:*

There is no currently proven therapy.

Potential treatments include lifestyle modifications to lose weight, insulin sensitizing agents (eg, metformin), and optimizing management of diabetes and dyslipidemia. Avoid hepatotoxins (alcohol and large doses of acetaminophen).

#### *Future burdens:*

Both obesity and diabetes are increasing. An increase in NAFLD is also anticipated.

#### *Conclusion:*

Cryptogenic cirrhosis is a significant contributor to liver related morbidity. NAFLD is the most common cause of CC. The diagnosis of cirrhosis in these patients is usually delayed by almost a decade and is often not established until after the patient develops hepatocellular carcinoma or other complications of advanced liver disease. Once cirrhosis is diagnosed, mortality is greater than that of hepatitis C virus related cirrhosis.

Comment:

- 1 Is low intake of alcohol harmful in some persons? I would proscribe it.
- 2 See citations 1,2,3 in the article for studies presented in *Hepatology*.

This is a new concept to me. I wonder—is CC due to NAFLD really that common?

The disease is a spectrum, progressing from non-alcoholic hepatic steatosis, to non-alcoholic steatohepatitis, to increasing liver cell damage and cryptogenic cirrhosis. These stages seem to blend into each other.

As noted by the number of tests done for other unusual causes of liver disease, NAFLD is a diagnosis of exclusion. The pathogenesis of NAFLD is not clear.

Primary care clinicians have an opportunity to prevent end stage NAFLD by preventing and treating non-alcoholic hepatic steatosis and steatohepatitis. (Control of obesity, lipids, and diabetes.) RTJ

Coleman D Carter, M.D. provided an original abstract of this paper. He comments:

Findings of fatty liver on biopsy plus mild liver enzyme changes are not uncommon and frequently dismissed as not clinically significant. While this may be true in a majority of such patients, the realization that those changes may progress to advanced disease at a rate similar to hepatitis C (10% - 20%) warrants attention, particularly in obese patients with type 2 diabetes. CDC

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### ***Ambulatory BP Predicted Cardiovascular Outcomes More Accurately Than Office BP***

#### **6-9 PROGNOSTIC VALUE OF AMBULATORY BLOOD PRESSURE RECORDINGS IN PATIENTS WITH TREATED HYPERTENSION**

Do ambulatory BP (ABP) measurements in patients with *treated hypertension* predict cardiovascular events (CVE) independent of (ie, more accurately than) BP measurements obtained in the physician's office?. There is a lack of data comparing prognostic value of ABP in patients receiving active treatment of hypertension in whom both ABP and office BP are recorded.

This study prospectively compared associations between base-line ABP and office BP in treated patients with hypertension and subsequent CVE over 5 years.

Conclusion: ABP predicted CVE more accurately than office BP.

#### **STUDY**

1. Followed over 1900 patients (mean age 57) over a median of 5 years.
2. All had hypertension--defined as a mean of 3 sphygmomanometric (office) measurements done on two separate occasions, after 5 minutes of rest sitting in a chair, in which diastolic BP exceeded 90 mm Hg in a patient who was currently taking antihypertension drugs. Or 95 in patients who were not taking antihypertension drugs.
3. All patients entered into the study after being on drug therapy for at least 3 months. Thus, all had established hypertension and were receiving drug therapy. The choice of drugs was at the discretion of each physician. Attempts were made to treat to a target of 140/90.
3. ABP was recorded one time at baseline for 24 hours during the patient's normal daily activities. Readings

were recorded every 30 minutes between 8 AM and 8 PM, and at intervals of 60 minutes between 8 PM and 8 AM.

4. Compared outcomes at various levels of office BP and ABP. Primary endpoint= fatal and non-fatal cardiovascular events.

## RESULTS

1. Over 5 years, CVE occurred in 157 patients. As expected, both office and ABP of systolic and diastolic BP significantly predicted the primary endpoint--fatal and non-fatal cardiovascular events.
2. To determine outcomes, the investigators arbitrarily divided ABP patients into 2 groups: mean systolic BP < 135. and mean systolic BP 135 and higher. In both groups mean ABP was lower than office BP.

	< 135 (n = 1153)	135 and higher (n = 810)
Mean office BP	148/91	165/96
Mean ABP 24-h	124/78	148/90

3. Over 5 years, ABP under 135 predicted lower incidence of CVE than ABP 135 and higher.

	< 135 (n = 1153)	135 and higher (n = 810)
Fatal or non-fatal CVE	4.8%	12.4%
Fatal or nonfatal MI or stroke	1.9%	4.7%

4. ABP gave important clinical information as compared with office BP measurement:

- A. After multiple adjustments of various risk factors ABP independently and more accurately predicted incidence of CVE than office BP:

Office BP compared with ABP under 135 systolic and 135 and over:

Incidence of CVE	Office BP < 140	Office BP 140-158	Office BP 160 and above
24-h ABP < 135	3.7%	4.5%	7.0%
24-h ABP > 135	11.2%	7.0%	14.8%

*(At any level of office BP an ABP less than 135 predicted a better prognosis than a ABP over 135)*

- B. At any office BP, ABP over 135 predicted poorer prognosis than ABP under 135:

Incidence of CVE per 1000 person-years:

Office systolic	< 140	140-159	160 and above
ABP > 135	18	14	24
ABP < 135	6	7	12

*(My calculations from figure 2 p 2413 RTJ)*

- C. ABP may determine that some patients are being treated adequately despite high office BP:

Some individuals (23 of 790) had an ABP under 135 despite having an office BP 140-159, and some (19 of 796) had an ABP under 135 despite an office BP over 160.

*(Drug therapy need not be increased in these patients)*

## DISCUSSION

1. In patients already being treated for high BP, after adjustment for classical risk factors, including office BP, 24-hour ABP provided additional prognostic information including stroke and a combined outcome of non-fatal and fatal MI.
2. These results clearly demonstrate the limitations of office readings as routinely obtained.
3. The investigators suggest that if office determination of BP is relied upon, it should be done by repeated, standardized, conventional readings obtained at prespecified intervals. Otherwise, assessment may be misleading.
4. Patients enrolled in this study were not optimally treated, as judged by their office BP. Only 25% had systolic under 140. Yearly follow-up visits failed to show improvement.<sup>1</sup>

## CONCLUSION

In patients with *treated* hypertension, a higher ABP, systolic or diastolic, predicted cardiovascular events even after adjustment for classic risk factors including office BP. As judged by ABP, office BP may be misleading.

NEJM June 12, 2003; 2407-15 Original investigation, “The Office Versus Ambulatory Pressure Study”, first author Denis L Clement, Ghent University, Ghent Belgium [www.nejm.org](http://www.nejm.org)

### Comment:

Would periodic ABP measurement improve outcomes? Probably so, by indicating changes in therapy and adding to interest and compliance by the patient. RTJ

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### ***May Determine If Some Patients Are Overtreated Or Undertreated.***

## **6-10 AMBULATORY BLOOD-PRESSURE MONITORING IN CLINICAL PRACTICE**

*This editorial comments and expands on the preceding article.*

ABP has a highly reproducible circadian profile, with higher values when the patient is awake and mentally and physically active, lower values during rest and sleep, and an early-morning surge lasting 3 to 5 hours during the transition from sleep to wakefulness.

24-hour ABP monitoring yields readings during all the patient’s activities, and gives a far better representation of the “blood pressure burden” than that obtained during office visits.

Gaining acceptance of this technique in general practice has been difficult. Experts in cardiovascular medicine have been uncomfortable with the relegation of the office-based measurement of BP to secondary importance. After all, office BP values have been used in major clinical trials of cardiovascular outcomes as well as in practice for years. But, office BP measurements have clinically relevant shortcomings. In today’s rushed practice, repeated measurements over a period of several minutes are the exception rather than the rule. A “white coat effect” (an increase in BP only in the medical care environment) is reported in as many as 20 to 35% of patients in whom hypertension is diagnosed.

The preceding study reported that subjects with a mean 24-h systolic ABP 135 and over when they were receiving drug treatment were nearly twice as likely to have a cardiovascular event as those with a mean systolic ABP under 135, regardless of their office BP. ABP may determine that many patients are undertreated. ABP may also determine that drug therapy is not necessary and may be discontinued or tapered.

Recent prospective cohort studies have shown that persons whose office BP is elevated, but whose mean 24-h ABP is below 130/80 are no more likely than normotensive persons to have a cardiovascular event.

ABP should be used more often in clinical practice. Self-monitoring at home and at work can be used to assess whether there is a large disparity between the office and out-of-office BP before ABP monitoring is considered.

“For those whose ambulatory blood pressure is truly normal (< 130/80) despite an elevated office blood pressure, and in whom there is no evidence of other cardiovascular risk factors of target-organ disease, avoidance of unnecessary drug therapy would be a clear benefit of the monitoring procedure.”

NEJM June 12, 2003; 348: 2377-78 Editorial by William B White, University of Connecticut School of Medicine, Farmington [www.nejm.org](http://www.nejm.org)

Comment:

ABP would serve two important functions: 1) In untreated patients whose office BP is high, ABP would determine if it is due to the “white coat effect”, 2) In drug-treated patients, it would determine if the patient is being overtreated, undertreated, or optimally treated. RTJ

The editorialist comments that research on the prognostic value of ABP led to the introduction, in late 2001, of Medicare coverage for ABP monitoring to assess patients with white coat hypertension.

The optimal lowest cut point for ABP is not yet fully determined--130/80 seems to be a reasonable goal at this time. I believe, like office BP, any reduction up to a defined low cut-off point will lead to a better prognosis, and any increase will lead to a less favorable prognosis. RTJ

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### ***Hard As We Try, We Just Can't Make Antioxidants Work***

## **6-11 USE OF ANTIOXIDANT VITAMINS FOR THE PREVENTION OF CARDIOVASCULAR DISEASE**

Oxidized low density lipoprotein is thought to play an important part in the pathogenesis of atherosclerosis. Observational studies have associated vitamin E and beta-carotene with reductions in cardiovascular events (CVE). Clinical trials have not. Indeed, small randomized studies have suggested a potential harmful effect in patients with coronary disease.

This meta-analysis of randomized trials assessed effects of these compounds on long-term cardiovascular disease mortality and morbidity.

Conclusion: There was a consistent lack of benefit.

### **STUDY**

1. Analyzed 7 randomized trials of vitamin E and 8 trials of beta-carotene. All trials included 1000 or

more subjects. (Total of 81 000 and 138 000.)

2. Dose ranged from 50-800 IU for vitamin E, and 15-50 mg beta-carotene.
3. Follow-up = up to 12 years.

## RESULTS

1. Vitamin E did *not* provide benefit in mortality compared with control treatment (11.3% vs 11.1%). It did not significantly reduce risk of cardiovascular death or cerebrovascular accident.
2. Beta-carotene was associated with a small but significant *increase* in all-cause mortality and a slight *increase* in cardiovascular death.

## DISCUSSION

1. With the exception of one trial, the tendency toward increase in death associated with beta-carotene was strikingly consistent across all major trials including diverse populations.
2. “Our findings are especially concerning given that the relevant beta-carotene doses are commonly used in preparations of over-the-counter vitamin supplements and are included in readily available multivitamin supplements that have been advocated for widespread use.”
3. The initial enthusiasm for the clinical use of anti-oxidant vitamins for prevention of CVD stemmed from preclinical studies. Animal data suggested benefit in prevention of atherosclerotic progression. The early findings and the presumed safety of antioxidant supplementation led to large prospective cohort studies in which the association between antioxidant vitamin intake and improved cardiovascular outcomes were reported. However, these findings were not confirmed in randomized trials. This suggests confounding.
4. Cigarette smoking destabilizes the beta carotene molecule, resulting in up regulation of growth factors associated with tumorigenesis. Beta carotene has adverse effects on lipids. Vitamin E in one large study blunted the HDL-raising effect of simvastatin and niacin, and lessened their protective effect. Others have challenged the suggestion that vitamin E is a potent in-vivo inhibitor of LDL oxidation.

## CONCLUSION

A lack of beneficial effect was seen consistently for various doses of these two vitamins in diverse populations. The routine use of vitamin E is not supported. The use of beta carotene is associated with a small but significant excess of all-cause mortality and cardiovascular death.

Lancet June 14, 2003; 361: 2017-23 Original investigation, first author Deepak P Vivekananthan, Cleveland Clinic Foundation, Cleveland, Ohio. [www.thelancet.com](http://www.thelancet.com)

See also “Incidence of Cancer and Mortality Following alpha-Tocopherol and beta-Carotene Supplementation” JAMA July 23/30 2003; 290: 475-85. This 8-year postintervention follow-up assessment of cancer incidence and cause-specific mortality concerned over 25 000 men. All were smokers age 50-69 at baseline. Compared with non-recipients, overall relative risk of lung cancer was 1.06 among recipients of beta-carotene. (Ie, risk was increased) The RR for prostate cancer was 0.88. (Possible benefit)

No late preventative effects on other cancers were observed. RR of death was slightly higher in recipients.

“Smokers should avoid beta-carotene supplementation.”

Comment:

My daily supplement contains 5000 IU beta-carotene. One IU = 0.6 micrograms. 5000 IU = 3 milligrams, considerably less than the doses quoted in the study.

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## **6-12 EFFECTIVENESS OF NEURAMINIDASE INHIBITORS IN TREATMENT AND PREVENTION OF INFLUENZA A AND B**

The neuraminidase inhibitors zanamivir (*Relenza*) and oseltamivir (*Tamiflu*) are active against influenza A and B. They are less likely to cause adverse effects than the older antivirals.

This systematic review assessed clinical effectiveness of both drugs for treatment and prevention of influenza A and B.

Conclusion: Both drugs are clinically effective for treating and preventing influenza.

### **STUDY**

1. Systematic review of randomized trials considered 17 treatment trials and 7 prevention trials.
2. All trials compared one of the drugs vs placebo or standard care. Doses and duration of therapy varied.
3. For *treatment*:

Zanamivir was given by intranasal inhalation, typically 10 (two inhalations) mg twice daily for 5 days.  
(total of 20 inhalations)

Oseltamivir given orally -- typically 75 to 150 mg twice daily for 5 days.

Drugs must be given within 48 hours of onset of symptoms.

4. For *prevention*:

Zanamivir typically given 10 mg by inhalation once or twice daily for up to 4 weeks.

Oseltamivir 75 mg orally once or twice daily for up to 6 weeks in adults and adolescents over age 12. Duration of therapy varied from 5 days to 6 weeks.

5. Main outcomes measures = median time to alleviation of symptoms (for treatment trials) and number of flu episodes avoided (for prevention trials).

### **RESULTS**

1. *Treatment*: of children and otherwise healthy individuals with zanamivir reduced the median duration of symptoms by one day. Oseltamivir reduced it by 0.9 days.
2. *Treatment* provided 29% to 43% relative reductions in the odds of complications requiring antibiotics when given within 48 hours of onset of symptoms.  
(*Complications were mainly lower respiratory infections, chiefly bronchitis. In how many patients were antibiotics really indicated? RTJ*)
3. *Prevention*: Both zanamivir and oseltamivir given prophylactically resulted in a relative reduction of 70-90% in the odds of developing flu.

(As usual, relative risk reductions are misleading. See comments for absolute risk reductions. RTJ)

4. Adverse effects: both were well tolerated; adverse effects few--nausea and vomiting the most common.

## DISCUSSION

1. Treating otherwise healthy adults and children with either drugs reduced duration of symptoms by between 0.4 and 1.0 days. They also reduced incidence of complications requiring antibiotic treatment.
2. Prevention strategies have varied considerably—in duration and dose. There is, however, lack of evidence for use in young children and in frail elderly people in residential care.

## CONCLUSION

Evidence consistently supports the view that both drugs are clinically effective in treating and preventing flu. Evidence is limited for treatment of certain populations as well as for prevention strategies.

BJM June 7, 2003; 326: 1235-39 Original investigation, first author Nicola J Cooper, University of Leicester, UK.

[www.bmj.com/cgi/content/full/326/7401/1235](http://www.bmj.com/cgi/content/full/326/7401/1235)

An accompanying commentary (pp 1249-40 by Lucy Hansen, University of Edinburgh) concerned the need to determine who benefits most from flu treatments:

No studies have compared the response to treatment in vaccinated vs unvaccinated elderly residential patients. One study of vaccinated patients reported a 92% relative reduction. We often forget that the vaccine is only 70% effective, and has only short term benefits. “Rather than neuraminidase inhibitors being an alternative to vaccination, they might be an additional treatment in high risk groups, particularly during epidemics or local outbreaks.”

Comment:

I believe there may be a limited application of these drugs. Oral *Tamiflu* (oseltamivir) would seem to be more advantageous. It is easier to take and more acceptable to patients. Choosing individuals for whom the drugs are indicated would be a clinical-judgment call, depending largely on cost, personal preference, and likelihood of severe complications from flu.

This is another study citing misleading relative reductions in risk rather than absolute reductions. The 2003 PDR provides additional information:

Gives no indication for use of zanamivir for prophylaxis.

Prophylactic oseltamivir given for up to 42 days in community outbreaks reduced infection incidence from 4.8% to 1.2%. Given in nursing home residents, reduced infection rate from 4.2% to 0.4%. (The majority of these had received vaccine.) For household contacts, incidence reduced from 10% to 1%.

The number needed to treat to prevent one person from getting flu varied from 11 to 28.

The results cited in the article are tenuous, especially those citing effects of the drugs in preventing complications which result in antibiotic use.

*Tamiflu* costs \$60 for 75 mg twice daily for 5-days

*Relenza* diskhaler costs \$48 for 5 mg inhaled twice daily for 10 days. (total of 20 inhalations)

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## *Does Not Imply Inexorable Progression Of Nephropathy*

### **6-13 REGRESSION OF MICROALBUMINURIA IN TYPE 1 DIABETES.**

Previous studies suggested that microalbuminuria in patients with type 1 diabetes heralds an inexorable process leading to overt proteinuria.

Other studies have questioned this assumption

This natural history study was designed to identify the determinants of the early stages of diabetic nephropathy in type 1 diabetes, and to determine the frequency of occurrence of a significant reduction in urinary albumin excretion (regression). It determined factors affecting such a reduction in patients with microalbuminuria.

Conclusion: Regression of microalbuminuria frequently occurred.

### **STUDY**

1. Prospective study included 386 patients with type 1 diabetes. All had persistent microalbuminuria.  
(Mean duration of diabetes = 18 years; mean age = 30)
2. Microalbuminuria defined as albumin excretion of 30 to 300 micrograms per minute (43 to 430 milligrams per 24 hours).
3. Patients were checked every 2 years. Regression was defined as a 50% reduction in urinary albumin excretion from one two-year period to the next.

### **RESULTS**

1. Regression of microalbuminuria was frequent. Over 6-years, 58% regressed. Only 19% went on to overt proteinuria over a 6-year follow-up.
2. Use of angiotensin-converting-enzyme inhibitors was *not* associated with regression.  
(See following discussion.)
3. Several factors were independently associated with regression: microalbuminuria of short duration (younger age); HbA1c levels under 8%; systolic BP under 115 mmHg; and low levels of both total-cholesterol (< 198 mg/dL) and triglycerides (< 145 mg/dL).
4. Patients with favorable levels of all modifiable risk factors were more likely to regress.

### **DISCUSSION**

1. Microalbuminuria in patients with type 1 diabetes has been considered the first step toward proteinuria and renal failure. Yet, the results of this study indicate that microalbuminuria is more likely to subside to normal than to progress to overt proteinuria.
2. "The evolution of early diabetic nephropathy may not be confined to a single pathway leading to progression of proteinuria."
3. When elevated urinary albumin excretion develops in persons with type 1 diabetes, it can remain static, advance toward proteinuria, or regress toward more normal levels.
4. Given the well-established role of hyperglycemia as a risk factor, it is not surprising that HbA1c

below 8% were associated with regression. Frequency of microalbuminuria rises steeply as HbA1c levels rise.

5. The association with lipid abnormalities provides additional rationale for use of statin drugs even in patients with type 1 diabetes who are not considered to have dyslipidemia.
6. The authors suggest that frequent screening for microalbuminuria may lead to more effective interventions.
7. In short-term studies, ACE inhibitors retard the increase in urinary albumin excretion. "ACE inhibitors are now well established for prevention of progression of microalbuminuria to proteinuria. In the present study ACE inhibitors were not associated with *regression* of microalbuminuria. The biologic mechanisms of progression and regression may differ."

## CONCLUSION

Urinary albumin excretion does not imply inexorable progression of nephropathy. Regression frequently occurs, associated with lower HbA1c levels, lower BP, and lower levels of cholesterol and triglycerides.

NEJM June 5, 2003; 348: 2285-93 Original investigation, first author Bruce A Perkins, Joslin Diabetes Center, Boston, Mass. [www.nejm.org](http://www.nejm.org)

### Comment:

When extrapolated to type 2 DM, these results give a much more optimistic prognosis than previously thought. Frequent testing for microalbuminuria may lead to earlier and stricter control of multiple risk factors in individual patients, including HbA1c levels. Diagnosing microalbuminuria requires multiple tests over time. RTJ

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### *A Potentially Important Aid In Approach To Treatment.*

## **6-14 NONINVASIVE DETECTION OF CLINICALLY OCCULT LYMPH-NODE METASTASES IN PROSTATE CANCER.**

Accurate detection of lymph-node metastases in prostate cancer (**PC**) is an essential component of the approach to treatment.

MRI by itself provides images with excellent detail and soft tissue contrast, but is relatively insensitive for the detection of lymph-node metastases.

This study investigated whether highly lymphotropic super-para-magnetic nano-particles (LSPMNP) could be used in conjunction with high-resolution magnetic resonance imaging (**HR-MRI**) to reveal small nodal metastases. These iron-containing nanoparticles are given intravenously. They slowly extravasate from the vascular into the interstitial space, from which they are transported to lymph nodes by way of lymphatic vessels. Within the lymph nodes, the particles are internalized by macrophages. They change the magnetic properties and are then more clearly detected by MRI. They may provide visualization of metastatic disease in lymph nodes which are not enlarged. (Clinically occult disease).

Conclusion: Use of MRI in patients given magnetic nanoparticles allowed detection of small and otherwise undetectable metastases.

## STUDY

1. Enrolled 80 patients with clinical stage T1, T2, and T3 PC. (Increasing size of the primary cancer).
2. All underwent surgical lymph-node resection or biopsy.
3. All were examined by HR-MRI before and HR-MRI 24 hours after intravenous administration of the iron containing particles.
4. Imaging results were correlated with histopathological findings.

## RESULTS

1. On a patient-by-patient basis, of the 80 patients, histologically detected metastases were present in 33 patients (41%).  
The new MRI screening detected metastases in all 33. (Sensitivity of the test = 100%; no false negative tests)  
There were a few patients without metastases who demonstrated a positive MRI. (Specificity of the test = 97%; few false positives.)
2. 334 lymph nodes were resected or biopsied. On a node-by-node basis, 63 nodes had histologically detected metastases. Of these 63, 71% did not fulfill the usual imaging criteria for malignancy. The HR- MRI detected 90% of these nodes. (Sensitivity = 90%; few false negatives.)

## DISCUSSION

1. In this study, HR-MRI after administration of the iron particles correctly identified *all* patients with nodal metastases.
2. Patients with truly localized PC have the options of radical prostatectomy, watchful waiting, and radiotherapy. In men with locally advanced or metastatic disease, adjuvant androgen-deprivation therapy with radiation is the mainstay of management.
3. Compared with non-enhanced HR-MRI, sensitivity was increased from 45% to 100%. (No false negatives.) Specificity was 97% (Few false positives)
4. Even small metastases—less than 2 mm in diameter—were occasionally identified within normal-sized lymph nodes. These are below the threshold for detection by any other imaging techniques.

## CONCLUSION

High resolution MRI with magnetic iron-containing nanoparticles allowed detection of small and otherwise undetectable lymph-node in patients with metastatic PC.

Comment:

Although this may not be applicable to primary care practice at this time, I believe it to be a major advance in diagnosis and treatment of PC. It may save many men from radical prostatectomy who have no chance at cure from surgery. It may reassure many that they do not have advanced disease. RTJ

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**Keep Mentally Active As You Age!**

**6-15 LEISURE ACTIVITIES AND THE RISK OF DEMENTIA IN THE ELDERLY**

Participation in leisure activities has been associated with a lower risk of dementia in the elderly. Prior studies reported an association between dementia and reduced participation in leisure activities in midlife.

Persons with higher educational levels are more resistant to the effects of dementia. They may have greater cognitive reserve and increased complexity of neuronal synapses. Participation in leisure-time mental activities may lower the risk of dementia by improving cognitive reserve.

In most types of dementia there is a long period of cognitive decline preceding the diagnosis. This study concerned the influence of leisure activity during this preclinical period on risk of developing dementia

Conclusion: Frequent participation in leisure-time mental activities was associated with reduced risk of dementia and rate of decline in memory.

**STUDY**

1. Prospective observational study followed 469 subjects. At baseline, they were between 75 and 85 (mean = 79; middle class; mostly white and female). All were living in the community. None had dementia.
2. Determined the frequency of participation in leisure activities at enrollment. Constructed cognitive-activity and physical-activity scales in which units of measurements were activity-days per week.
3. Interviewed subjects at baseline regarding participation in 6 cognitive activities: reading books or newspapers, writing for pleasure, doing cross-word puzzles, playing cards and board games, participating in organized group discussions, and playing musical instruments.
4. Eleven physical activities were also assessed.
5. Evaluated risk of development of dementia according to baseline level of participation in leisure activities with adjustments for age, sex, educational level, presence or absence of chronic medical illnesses, and baseline cognitive status.

**RESULTS**

1. Over a median follow-up of 5 years, dementia developed in 124 subjects ( Alzheimer’s in 61; vascular dementia in 30; mixed in 25, others in 8).
2. Among leisure activities, reading, playing cards and board games, playing musical instruments, doing cross-word puzzles, and dancing were associated with a reduced risk of dementia.

Hazard ratio\* of various activities (compared with rare participation):

Frequently playing games	0.26
Frequent reading	0.65

Frequent musical instruments 0.31

Frequent crossword puzzles 0.59

*(\* Individuals age 75-85 who remained mentally active in various ways had about one quarter to two thirds the risk of developing dementia over 5 years.)*

3. A one-point increment in the cognitive-activity score was significantly associated with a reduced risk of dementia. (Hazard ratio = 0.93).
4. Results were similar for Alzheimer's and vascular dementia.
5. Increased participation in cognitive activities at baseline was also associated with reduced rates of decline in memory.
6. Increments in physical activity (except for dancing) were not associated with reduced risk.

## DISCUSSION

1. The study demonstrated a significant association between a higher level of participation in leisure-time mental activities at baseline and decreased risk of dementia—both Alzheimer's and vascular.
2. A one point increment in the cognitive activity score, which corresponds to participation in an activity for one day per week, was associated with a reduction of 7% in the risk of dementia. Participants who worked cross word puzzles four days a week had a risk that was 47% lower than among subjects who did puzzles only once a week.
3. The association remained robust even after adjustment for potential confounding variables such as age, sex, education, presence of medical illness, and baseline cognitive status.
4. Subjects with scores in the highest third on the cognitive-activity scale (more than 11 activity-days per week) had a risk of dementia 63% lower than that among than subjects in the lowest third.
5. Participation in leisure time mental activities may increase cognitive reserve, and delay onset of memory loss and dementia.

## CONCLUSION

Frequent participation in leisure-cognitive activities was associated with a reduced risk of dementia and reduced rate of decline in memory.

NEJM June 19, 2003; 348:2508-16 Original investigation, first author Joe Vergese, Albert Einstein College of Medicine, Bronx, New York. [www.nejm.org](http://www.nejm.org)

An editorial in this issue of NEJM (pp 2489-90 by Joseph T Coyle, Harvard Medical School) comments:

One hypothesis put forward about the mechanism of protection is that of "cognitive reserve". Having greater intellectual resources may buffer the underlying damage associated with the early stages of dementia, thereby delaying the onset of symptoms. The brain has use-dependent plasticity. Effortful mental activity may not only strengthen existing connection, but stimulate neurogenesis. Persistent engagement by the elderly in effortful mental activities may promote plastic changes in the brain that circumvent the pathology underlying the dementia. Leisure activities at the very least, enhance the quality of life, and they just may do more than that.

Comment:

The study reported that increased cognitive activity was associated with delay and prevention of vascular dementia as well as Alzheimer's. We should not forget that, although we have not yet unraveled the pathogenesis of Alzheimer's, we already know a great deal about prevention of vascular dementia. We should do all we can to protect our brains as well as our hearts from vascular disease. Several recent studies abstracted in *Practical Pointers* relate to possible delay in development of dementia through measures to reduce risk of vascular disease (low-to-moderate consumption of alcohol, increased intake of fish, reduction in levels of homocysteine by folic acid, and control of blood pressure.) All of these have been observational studies subject to bias.

One interesting interventional study ("The Effects Of Cognitive Training Interventions With Older Adults" JAMA November 13, 2002; 288: 2271-81) reported that, in older adults, training sessions specifically aimed at memory (mnemonic strategies and exercises); inductive reasoning (problem solving); and at speed of processing (visual search skills and ability to identify and locate visual information quickly) improved cognitive abilities.

Several other studies reported a decline in cognitive impairment associated with increasing physical activity.

The possible benefits of cognitive activity and physical activity are still conjectural. Certainly it would be reasonable for elders to participate in both regularly. RTJ

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***Depression Is So Common, Primary Care Clinicians Should Screen For It.***

**6-16 AWARENESS ABOUT DEPRESSION: Important for All Physicians**

The June 18 issue of JAMA was devoted to papers on depression. This editorial addressed a range of issues from these papers and called for awareness on the part of virtually all physicians on this major public health problem.

1. A nationally representative household survey of the 48 contiguous United States found that the lifetime prevalence of major depression is 16%. Recognition and treatment of depression in primary care practice is woefully inadequate.
2. Seven percent reported major depression during the past year. This was associated with substantial symptoms and role impairment.
3. Fewer than 25% of those respondents received treatment meeting criteria for being at least minimally adequate.
4. The loss of productive time due to depression in the United States amounts to an estimated \$44 billion per year (not including treatment or disability costs). The majority of this was not absenteeism, but decreased performance.
5. The WHO supported study predicts major depression will become the second leading cause of disability by 2020 (second only to ischemic heart disease).
6. Strategies must be adaptable culturally to address this global problem.
7. The etiology and pathophysiology of depression have not been precisely defined. This makes it difficult to define remission following treatment and to identify those with recurrent and chronic disease.
8. Positron emission tomography (PET) has revealed decreased brain activity in selected regions following chemically induced depression. This raises the possibilities of objective measures of remission and vulnerability to relapse.

9. Just as they ignore depression in their patients, physicians ignore depression in themselves. There are significant personal and professional stigma and institutional obstacles that prevent physicians from seeking treatment.
10. Depression is usually a recurrent or chronic disease. The goal of therapy should be complete and permanent remission.

JAMA June 18, 2003; 289: 3169-70 Editorial by Richard M Glass Deputy Editor JAMA [www.jama.com](http://www.jama.com)

*Abstracted by Coleman D. Carter, M.D.*

Comment:

Depression is so common, I believe primary care clinicians should screen for it, as they screen for alcohol abuse, hypertension, diabetes and other common diseases. Depression is treatable. Some valid screening instruments are simple. Screening instruments are available on the internet <http://intelihealth.com/depressiontest> (Accessed July 26 )

Depression is common in physicians. Suicide is a disproportionately high cause of mortality in physicians, especially females. RTJ

## **6-17 ASPIRIN AND TICLOPIDINE FOR PREVENTION OF RECURRENT STROKE IN BLACK PATIENTS: A Randomized Trial**

Afro-Americans are disproportionately affected by stroke. They have a different prevalence of cardiovascular risk factors and different biological manifestation of risk factors (eg, low renin hypertension).

Almost all trials for stroke prevention have been based on populations with few Afro-Americans. Previous studies have suggested that the platelet-aggregation inhibitor ticlopidine (*Ticlid*) is more effective (particularly in Afro-Americans) than aspirin in the prevention of recurrent stroke. The current study was designed to test that hypothesis.

Conclusion: Ticlopidine was *not* more effective than aspirin in preventing recurrent stroke in Afro-Americans.

STUDY:

1. Randomized, double-blinded, multicenter trial of 1809 Afro-American men and women who recently had a noncardioembolic stroke.
2. Randomized to: 1) ticlopidine 500 mg daily, or 2). 650 mg aspirin daily.
3. Primary endpoint was composite outcome of recurrent stroke, myocardial infarction, or vascular death.
4. Follow-up = 2 years.

RESULTS:

1. The primary outcome end point of recurrent stroke, myocardial infarction, or vascular death was reached by 15% of ticlopidine patients and 12% assigned to aspirin. (Absolute difference = 3%; NNT = 33.)

2. Outcomes	Ticlopidine (n = 902)	Aspirin (n = 907)
Recurrent stroke		
Fatal	4	2

Non-fatal	102	84
Myocardial infarction		
Fatal	1	0
Non-fatal	8	8
Vascular death	18	18
Death (all causes)	45	40

(No statistical difference between the 2 drugs.)

2. There was no significant difference in type or severity of stroke.
3. There were 270 serious adverse events with ticlopidine and 262 with aspirin.
4. The study was terminated when futility analysis showed less than 1% chance of proving superiority of ticlopidine.

#### DISCUSSION:

1. The study had a high drop-out rate which was expected due to the study population.
2. The primary event rates were lower than expected possibly due to increasing use of cholesterol-lowering agents during the study period.
3. Ticlopidine still ranks third in market share for antiplatelet prescriptions.
4. The costs, side-effects, and lack of superior efficacy do *not* support ticlopidine as first-line prevention therapy for recurrent stroke.

#### CONCLUSION

Aspirin is a better treatment than ticlopidine for aspirin-tolerant Afro-Americans with noncardioembolic ischemic stroke.

JAMA June 11, 2003; 289: 2947-2955 The African American Antiplatelet Stroke Prevention Study, first author Philip Gorelick, Rush Medical College, Chicago, IL [www.jama.com](http://www.jama.com)

Ticlid 500 mg (2 X 250 mg) costs \$2.86 \$86 a month.

#### Comment:

The authors and an accompanying editorial discussed the difficulty in recruiting and maintaining participants in a study when they are from lower socioeconomic groups that have limited interaction with, and distrust of the medical establishment.

#### CDC

I am always pleased when I learn that an old, very inexpensive drug is superior to a new, very expensive one, RTJ

*(Note: the major points of this study were abstracted by Coleman D Carter, M.D.)*













