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FOR PRIMARY CARE

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ALL ADULTS IN THE USA HAVE AT LEAST ONE RISK FACTOR FOR CVD

TREATMENT REDUCES RISK OF CVD REGARDLESS OF THE INITIAL LEVEL OF THE RISK

SHOULD WE NO LONGER USE THE TERM “HYPERTENSION”?

MORPHINE + GABAPENTIN EFFECTIVE FOR TREATMENT OF NEUROPATHIC PAIN

IS ADDING CLOPIDOGREL TO ASPIRIN BENEFICIAL IN PATIENTS WITH ACUTE MI?

LOW DOSE ASPIRIN FOR PRIMARY PREVENTION OF CVD IN WOMEN.

WARFARIN OR ASPIRIN BEST FOR TREATING INTRACRANIAL STENOSIS?

VITAMIN D DEFICIENCY RELATED TO MUSCLE WEAKNESS

FOLATE (REDUCING HOMOCYSTEINE LEVELS) TO PREVENT RISK OF FRACTURE

IS THERE ANY HOPE FOR VITAMIN E?

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HIGHLIGHTS AND EDITORIAL COMMENTS MARCH 2005

Sorting out and critiquing the details of the three following abstracts was difficult and time-consuming. They point to a developing sea-change in our approach to prevention of atherosclerotic disease.

A new approach is based on the premise that:

- 1) Risk is lowered to some extent when each risk factor (clinical and lifestyle) is reduced, regardless of its initial level. The risk need not be lowered to “normal”.
- 2) When risk factors are lowered, the benefits are additive.

I believe the disease is largely preventable because the benefits achieved by reducing every modifiable risk factor (either by drugs or change in lifestyle) are additive. Risks are reduced linearly. There is no “normal” level. We should reduce all risk factors as safely and as economically as possible. This should replace our focus on only one or two risk factors (eg, lipids and blood pressure).

I believe a modest reduction in risk factors which we treat with drugs will, if lifestyle factors are reduced concomitantly, prevent cardiovascular events in millions of people in the USA.

Please read the 3 full abstracts. RTJ

All Adults in the USA Have One or More Risk Factors for Atherosclerotic Disease.

3-1 RELATIVE IMPORTANCE OF BORDERLINE AND ELEVATED LEVELS OF CORONARY HEART DISEASE RISK FACTORS

Prospective cohort study (The Framingham Study) and a national cross sectional survey (Third National Health and Nutrition Examination Survey) considered a large group of white, non-Hispanic persons between ages 35 and 74. (Mean age = 50)

Determined the first CHD event (defined narrowly as a myocardial infarction or cardiac death over 10-years) related to five major CHD risk factors: BP, LDL-cholesterol, HDL-cholesterol, glucose intolerance, and smoking.

Assigned three categories to each risk factor—elevated, borderline, and optimal.

	Optimal	Borderline	Elevated
Systolic BP	under120	120-139	over 139
Diastolic BP	under 80	80-89	over 89
LDL-cholesterol	under100	100-159	over159
HDL-cholesterol	over 59	59-40	under 40

Other borderline factors:

Impaired fasting glucose (110-123)

Past history of smoking

Other elevated risk factors

Diabetes

Smoking

Optimal levels of all 5 risk factors were rarely present in any age group or in either sex.

Seventy four % of men and 59% of women had one or more elevated risk factors. Twenty six % of men and 41% of women had at least one borderline risk factor. (Note: this adds up to 100%)

The authors estimate that, for ages 35-74, over a 10-year period, nearly 4.7 million white men and over 1 million white women in the US will experience a first MI or cardiac death. More than 90% of CHD events will occur in individuals with at least one elevated risk factor, and 8% in those with only borderline risk factors.

I believe this study presents too narrow a view of the cardiovascular disease problem in the US population. The study underestimates risk of atherosclerotic events.

- 1) *Ten years is too short a time to assess the overall risk of disease. The atherosclerotic process begins decades earlier and ends decades later.*
- 2) *Only 5 risk factors were considered. There are many others for which we should intervene: body mass index, dietary factors, physical fitness, intra-abdominal fat, triglycerides, C-reactive protein, abstinence from alcohol. The object of prevention should be to lower every individual risk factor as much as possible considering safety and cost. The number of risk factors far exceeds those chosen by the study.*
- 3) *The definition of disease was too narrow. (Only cardiac death and myocardial infarction). This eliminates consideration of other acute coronary syndromes, stroke, vascular dementia, peripheral vascular disease, and aortic aneurysm.*
- 4) *The study arbitrarily divided the cohort into 3 subgroups of risk—elevated, borderline and optimal and assumed the risk was equal in every individual in each cohort. The study did not consider the considerable differences in risk of disease associated with varying levels of the risk factors in each of the 3 groups. Risk rises and falls linearly. An individual with a LDL-cholesterol of 110 (borderline) has lower risk than one with a LDL-c of 145 (still borderline). A person with a systolic BP of 145 (elevated) is at much lower risk than one with a systolic of 175 (also elevated).*

This article tilts toward the traditional practice of screening to identify higher risk associated with a relatively few risk factors, and vigorously treating each individual risk factor. Is screening, and treating, and retesting every one of 5 “elevated” risk factors the best approach? This is certainly not practical when applied to the entire at-risk population. (Essentially the whole population in the USA.) How vigorously should “borderline” factors be treated?

All risk factors add to risk in all individuals in our high-risk culture. They should be treated empirically and lowered concomitantly. Laboratory testing may be minimized.

Atherosclerosis is an essentially preventable disease. We have failed miserably in our efforts to prevent it.

We need to apply a new population-based approach to prevention.

The approach changes for patients with established atherosclerotic disease. Risk reduction should be applied vigorously to all factors. RTJ

Drug And Lifestyle Modifications Are Beneficial Regardless Of The Initial Level Of The Risk Factor.

3-2 THE MIDDLE-AGED AND OLDER AMERICANS; Wrong Prototype for A Preventive Polypill?

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

Most Americans older than age 55 have one or more risk factors for cardiovascular disease” 1/3 or more have hypercholesterolemia, 1/5 smoke, most have inactive lifestyles, 1/3 have high BP. About 1/3 are obese, about 1/10 have diabetes.

Americans have a dizzying array of options to reduce risk. Preventive approaches aimed primarily at identifying and treating individual risk factors were popular in the 1980s and 1990s but had limited success.

Experts now recommend assessment of an individual’s *global* risk for vascular disease when deciding whether to treat risk factors, and when selecting specific target levels for those risk factors.

In 2003 Wald and Law¹ proposed a radical population-based strategy that they claimed would reduce cardiovascular disease by 80%, and have greater impact on public health than any other preventive strategy. They advised discarding the view that risk factors need to be measured (and treated individually if found to be ‘abnormal’). Instead they advocated treating *all* adults older than age 55 with a “Polypill” containing low doses of a statin, folic acid, aspirin, and 3 antihypertension drugs. (Low-dose presumably would be associated with fewer adverse effects.) This was based on the premise that risk factors are present in *everyone* in Western societies, and determination of individuals’ global risk is not necessary, and that 96% of deaths from vascular disease occur in people over age 55. Monitoring each individual’s risk factor level to assess treatment benefits is of limited usefulness.

Risk factor interventions with drugs and lifestyle modifications are effective whatever the initial level of the risk factor.

The editorialists comment that treating everyone older than age 55 with a low-dose Polypill without measuring risk factors may be too audacious for Americans. Adverse effects will likely occur from these multi-drug pills in low risk patients who have little potential for benefit.

When I first read of the Polypill, I thought the authors were suggesting the concept “tongue in cheek”. Subsequently the concept gained considerable attention and comment.

The premise of the Polypill:

- 1) All persons have risk factors for CVD. There is no cut point below which risk is not evident, and no cut point above which risk does not increase.*
- 2) The Polypill reduces 4 risk factors (BP, LDL-c, platelet aggregation, and homocysteine). The benefit from lowering all 4 is additive, although not equally.*

The Polypill is limited to drug therapy. And only in persons over age 55. The range of risk factors is much larger, and the atherosclerotic process begins at a much younger age. Many individuals experience a CVD event at an early age.

Each risk factor (lifestyle and clinical) adds to risk. When each risk factor is reduced, (even if only modestly) benefit increases additively.

Primary care clinicians and their patients tend to focus on measuring and treating only a few risk factors (eg, BP and cholesterol). Indeed “know your cholesterol” has become a national imperative. In the mind of the public achieving a “low” cholesterol is the best one can do to prevent CVD. But, individuals may have a LDL-c considerably below 100 and still be at high risk due to presence of other factors.

.What to do? 1) Treat everyone empirically, or 2) Treat only select individuals after screening. If you concede that everyone is at risk, you must choose 1). Treating everyone with drug therapy is too drastic a measure. Lifestyle measures begin at an early age and modifying them can reduce risk without adverse effects. More clinicians may now be encouraged to list all risk factors in their individual patients and point out the additive effect of lowering each of them.

I believe atherosclerosis is essentially a preventable disease. Our attempts at control are failing miserably. Americans refuse to adopt preventive lifestyles. Primary care clinicians have failed to adequately educate the public.

Once atherosclerotic disease becomes established, treatment changes to all-out reduction of risk factors. RTJ

A Practical Definition Of Hypertension: The Value Of BP Below Which No Further Benefit Of Lowering The BP Can Be Demonstrated

3-3 HYPERTENSION—TIME TO MOVE ON

In view of the *continuous* associations between BP and cardiovascular disease risks, the value of categorical systems for classifying BP is questionable. Such categorical systems provide little useful information about an *individual's* risk of actually developing a blood-pressure-related cardiovascular disease. Most guidelines acknowledge that risks are determined by many factors and not by BP alone.

A practical definition of hypertension is the value of BP below which no further benefit of lowering the BP can be demonstrated. There is now compelling epidemiological evidence of continuous associations between usual BP values down to about 115/75 and risks of major cardiovascular disease. Non-hypertensive individuals with multiple risk factors or a history of cardiovascular disease will often be at higher *absolute* risk of BP-related cardiovascular events than hypertensive patients without other risk factors.

“So why do we persist with this focus on the treatment of hypertension (defined arbitrarily) rather than the prevention of blood-pressure-related diseases?”

This reinforces the argument presented in the preceding article—risk factors are additive and should not be considered alone.

The Combination Was Associated With Significantly Less Pain-Related Interference with Mood, And Higher Scores for Vitality and Social Functioning

3-4 MORPHINE, GABAPENTIN, OR THEIR COMBINATION FOR NEUROPATHIC PAIN

This study assessed the effectiveness of a combination of morphine + gabapentin vs either alone and placebo for pain due to diabetic neuropathy and post-herpes zoster neuralgia.

Treatment with a combination of morphine + gabapentin resulted in greater relief of pain than treatment with either alone.

	Baseline	Placebo	Gabapentin	Morphine	Morphine + gabapentin
Mean daily pain scores On a scale of 1 to 10	5.7	4.5	4.2	3.7	3.06
McGill Pain Questionnaire On a scale of 0 to 45	18.9	14.4	10.7	10.7	7.5

The maximum doses of morphine and gabapentin were lower with the combination than for each given separately.

The combination was associated with significantly less pain-related interference with mood, and higher scores for vitality and social functioning. The combination was also associated with improvement in depression as measured by the Beck Depression Inventory.

This may bring considerable relief to some patients with very disturbing pain.

Gabapentin(Neurontin) is an analogue of butyric acid. It modulates calcium channel subunits thought to be important in neuropathic pain. It has both analgesic and anti-convulsant action and is approved for treatment of partial seizure epilepsy and post-herpetic neuralgia.

Gabapentin and morphine have mechanically distinct analgesic actions. The combination may result in synergistic or additive pain relief at lower doses and with fewer side effects.

Repeated administration of gabapentin does not lead to tolerance.

Addition of Clopidogrel Improved Patency of The Affected Artery and Reduced Ischemic Complications.

3-5 ADDITION OF CLOPIDOGREL TO ASPIRIN AND FIBRINOLYTIC THERAPY FOR MYOCARDIAL INFARCTION WITH ST-SEGMENT ELEVATION

A substantial proportion of patients receiving fibrinolytic therapy for MI with ST-segment elevation have inadequate reperfusion or re-occlusion of the infarct-related artery. Aspirin significantly improves outcomes. But, aspirin is a relatively weak antiplatelet agent. It has limitations. It irreversibly inhibits cyclo-oxygenase in platelets thereby inhibiting synthesis of thromboxane, a powerful promoter of platelet activation. It exerts no effect on thromboxane-independent mediators of platelet activation. Up to 30% of persons with coronary artery disease are relatively resistant or unresponsive to aspirin.

Clopidogrel (*Plavix*) acts differently from aspirin in inhibiting activation and aggregation of platelets. Does addition of clopidogrel benefit patients with acute ST-segment elevation MI who are receiving fibrinolysis and aspirin?

The short-time study enrolled over 3400 patients (mean age 57) who presented within 12 hours after onset of an acute ST-segment elevation MI. Randomized to: 1) clopidogrel (300 mg loading dose followed by 75 mg once daily), or 2) placebo.

Over a period of about a week, the addition of clopidogrel improved patency of the affected artery and reduced ischemic complications and death.

Treatment was not associated with an increased rate of major bleeding or intracranial hemorrhage.

Plavix has been extensively advertised to the public for ongoing use in patients with CVD. It is expensive. A 75 mg tablet costs almost \$4.

I believe primary care clinicians may provide a meaningful advanced therapeutic measure to a patient presenting to the office with an acute MI. While transfer to the hospital is arranged, the patient may be given: 1) full dose aspirin (325 mg); 2) clopidogrel (300 mg); 3) a statin drug; and 4) a beta-blocker. A few packets containing these drugs may be kept handy. .

The NNT to Prevent One Stroke is Very High

3-6 RANDOMIZED TRIAL OF LOW-DOSE ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN.

Use of aspirin in *primary* prevention in women is controversial. The current recommendations for use of aspirin in *primary* prevention in women are based on limited data.

The Women's Health Study was a large, randomized, double-blind placebo-controlled trial of low-dose aspirin in the primary prevention of cardiovascular disease among over 39 000 apparently healthy women followed for a mean of 10 years for major cardiovascular events.

For the entire group of women over age 45, aspirin reduced risk of ischemic stroke. It did not protect against myocardial infarction and death from cardiovascular causes until after age 65.

Women taking aspirin experienced significantly more GI hemorrhages (RR = 1.40)

By my calculation, between 500 and 900 individuals would need to be treated for 10 years to prevent one ischemic stroke. Is this clinically significant? - especially when the increased risk of hemorrhage is considered. RTJ)

Thus far, studies indicate that, in men, the prophylactic benefit against first occurrence of myocardial infarction is much greater than in women. But in men, aspirin does not provide primary protection against stroke.

Warfarin Provided No Benefit Over Aspirin. Was Associated With More Adverse Effects.

3-7 COMPARISON OF WARFARIN AND ASPIRIN FOR SYMPTOMATIC INTRACRANIAL STENOSIS.

Randomized, double-blind multicenter (59 sites) trial entered over 550 patients (mean age 63). All had experienced a TIA or a non-disabling stroke caused by angiographically verified 50% to 99% stenosis of a major intracranial artery (internal carotid, middle cerebral, vertebral, or basilar).

Randomized to: 1) warfarin—target INR of 2.0 to 3.0, or 2) aspirin 650 mg twice daily.

Warfarin provided no benefit over aspirin. It was associated with significantly higher rates of adverse events.

“Aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis.”

This is a good example of a pragmatic (real world of practice) trial. Difficulty in control of warfarin dosage may have been the cause of its lack of benefit.

The Benefit/Harm-Cost Ratio of Vitamin D May Be Very High

3-8 RECENT DEVELOPMENTS IN VITAMIN D DEFICIENCY AND MUSCLE WEAKNESS AMONG ELDERLY PEOPLE

Vitamin D deficiency is common in the elderly (especially in the house-bound and nursing home patients). Its prevalence is much greater than previously realized. It may be associated with poor muscle strength, and a tendency to fall, as well as osteomalacia.

Higher plasma levels of calcidiol are associated with muscle strength, physical activity, and ability to climb stairs. Lower levels of calcidiol are associated with falls among the elderly. A randomized trial reported a 47% reduction in falls and fractures in elderly women given 800 IU of vitamin D daily (compared with controls receiving calcium alone) over 12 months.

The author states that supplementation is often inadequate. 400 IU daily may be ineffective. In contrast, 800 IU has been shown to significantly reduce the risk.

Treatment with a supplement of 800 IU daily should be seriously considered.

It is important to remember that patients with kidney and liver disease require special consideration. The kidney is the first step in metabolism of cholecalciferol to calcidiol. And the liver is involved in the final conversion to the active hormone, calcitriol.

See also:

“Effect of vitamin D on falls” Practical Pointers April 2004 [4-5]

“Effect of four-monthly oral vitamin D supplementation on fractures and mortality in man and women living in the community” March 2003 [3-4]

“Occult vitamin D deficiency in postmenopausal U.S. women with acute hip fracture April 1999 [4-7]

The Benefit/Harm-Cost Ratio of Vitamin B12 and Folate May Be Very High

3-9 HOMOCYSTEINE AND FRACTURE PREVENTION

This issue of JAMA presents evidence that an elevated homocysteine level might be associated with brittle bones. The randomized trial of Japanese patients who had suffered hemiplegia due to stroke compared a group given folate and B12 (effectively lowering homocysteine levels) with a control group. The untreated group had 5 times the fracture rate as the treated group.

At baseline, patients had low levels of serum B12 and folate, and high levels of homocysteine. In the treatment group serum homocysteine fell by 38%; increased by 31% in the placebo group. Serum B12 and folate levels increased in the treatment group; fell in the placebo group.

Homocysteine is a simple sulfur-containing amino acid. Folate and B12 are co-factors involved in its metabolism. They facilitate conversion of homocysteine to methionine (another sulfur-containing amino acid).

Years ago, the genetic abnormality homocysteinuria was demonstrated to be associated with atherosclerotic disease and osteoporosis. Homocysteine acts as an atherogenic and thrombogenic agent. Increased levels are associated with coronary artery disease, cerebrovascular disease, peripheral arterial disease and deep-vein thrombosis.

A substantial portion of the elderly in the USA has a marginal sufficiency of folate.

Supplementation with B12 and folate reduces serum homocysteine levels.

The benefit/harm-cost ratio of folate and B12 supplementation may be very high. Both are relatively inexpensive and safe.

The study did not assess vitamin D and calcium intake, although intake of both is traditionally low in the elderly in Japan, as is the exposure to sunlight. Their benefit/harm-cost ratio in preventing fractures is high. This would lead to a reasonable recommendation to supplement the diets of the elderly with B12, folate, calcium and vitamin D.

Practical Pointers has abstracted a number of studies in the past 5 years which conclude that folic acid and B12 do reduce homocysteine levels and produce clinical benefits:

Homocysteine Levels and the Risk of Osteoporotic Fractures May 2004 [5-10]

Associated with reduced risk of congestive heart failure March 2003 [3-14]

Observing a reduction in dementia and Alzheimer's disease February 2002 [2-10]

Reducing risk of major cardiac events and restenosis after PTCA November 2001 [11-11]

An Increased Risk of Heart Failure Associated With Vitamin E.

3-10 IS THERE ANY HOPE FOR VITAMIN E?

Over the past 3 to 6 years, placebo controlled trials have consistently shown that commonly used antioxidant vitamins (E, C, and beta carotene, or a combination) do *not* significantly reduce overall cardiovascular events or cancer.

This editorial comments on a study which reports a 7-year follow-up on a trial of vitamin E (daily 400 IU of alpha-tocopherol—a natural source). The study was based on a cohort of patients age 50 to 75 who had established cardiovascular disease or diabetes. There was no statistical benefit from the vitamins in reducing risk of total cancer incidence or cardiovascular events.

A subgroup finding reported a possible *harmful* effect—an increased risk of heart failure associated with vitamin E.

“In nearly 60 000 patients studied to date, there is no compelling evidence that higher doses of vitamin E reduce cardiovascular risk or cancer”. Indeed, there is a hint that the antioxidant may increase risk of heart failure.

“Vitamin E supplements should *not* be used in patients with vascular disease or diabetes.”

The “antioxidant” theory has become entrenched in the minds of the public in the USA. It may take a while to un-entrench the idea. The editorialists comment that enthusiasts may continue to claim that vitamin E has a protective effect against specific cancers (lung, oropharyngeal and prostate.).

FULL ABSTRACTS MARCH 2005

Sorting out and critiquing the details of the three following abstracts was difficult and time-consuming. They point to a developing sea-change in our approach to prevention of atherosclerotic disease.

A new approach is based on the premise that:

- 1) Risk is lowered to some extent when each risk factor (clinical and lifestyle) is reduced, regardless of its initial level. The risk need not be lowered to "normal".
- 2) When risk factors are lowered, the benefits are additive.

I believe the disease is largely preventable because the benefits achieved by reducing every modifiable risk factor (either by drugs or change in lifestyle) are additive. Risks are reduced linearly. There is no "normal" level. We should reduce all risk factors as safely and as economically as possible. This should replace our focus on only one or two risk factors (eg, lipids and blood pressure).

I believe a modest reduction in risk factors which we treat with drugs will, if lifestyle factors are reduced concomitantly, prevent cardiovascular events in millions of people in the USA.

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All Adults in the USA Have One or More Risk Factors for Atherosclerotic Disease.

3-1 RELATIVE IMPORTANCE OF BORDERLINE AND ELEVATED LEVELS OF CORONARY HEART DISEASE RISK FACTORS

This study, based on data collected in the 1980s-90s, investigated the relative contributions of borderline (suboptimal but below current treatment thresholds) and elevated vascular risk factors to the CHD burden in the USA.

Conclusion: The great majority of Americans have elevated risk factors for cardiovascular disease. Borderline risk factors alone account for a small proportion of CHD events.

STUDY

1. Prospective cohort study (The Framingham Study) and a national cross sectional survey (Third National Health and Nutrition Examination Survey) considered a large group of white, non-Hispanic persons between ages 35 and 74. (Mean age = 50)
2. Determined the first CHD event (defined narrowly as a myocardial infarction or cardiac death) related to five major CHD risk factors: BP, LDL-cholesterol, HDL-cholesterol, glucose intolerance, and smoking.
3. Assigned three categories to each risk factor—elevated, borderline, and optimal.

	Optimal	Borderline	Elevated
Systolic BP	under120	120-139	over 139
Diastolic BP	under 80	80-89	over 89
LDL-cholesterol	under100	100-159	over159
HDL-cholesterol	over 59	59-40	under 40

Other borderline factors:

- Impaired fasting glucose (110-123)
- Past history of smoking

Other elevated risk factors

Diabetes

Smoking

4. Estimated the absolute rates of CHD events likely to occur in each of the 3 cohorts over a 10-year period.

RESULTS

1. *Risk factor profiles:*

Optimal levels of all 5 risk factors were rarely present in any age group or in either sex.

Seventy four % of men and 59% of women had one or more elevated risk factors. Twenty six % of men and 41% of women had at least one borderline risk factor. (*Note this adds up to 100%*)

Those that had one or more elevated risk factors also had one or more borderline risk factors.

2. *CHD event rates:*

Rates increased progressively from those seen in persons with only borderline risk factors to those seen in persons with increasing numbers of elevated risk factors.

In men, CHD event rates rose as the number of borderline risk factors increased.

Ten year absolute risk of myocardial infarction or cardiac death exceeded 10% in men older than age 45 at baseline who had any one elevated risk factor and borderline levels of the other 4 risk factors. And in those who had at least 2 elevated risk factors.

In women with 1 or more elevated risk factors, presence of any borderline risk factors further increased risk.

3. *Estimated population at high global risk in the USA:*

Over 1/3 of men age 35-74 would be categorized as being at increased global risk (the likelihood of over 10% of them having an event in the next 10 years). And 14% would be at extremely high risk (> 20% in 10 years)

Overall, 63% of men over age 55 would exceed the 10% risk of events over the next 10 years.

Overall, 13% of women over age 55 would exceed the 10% threshold.

4. *Projected burden of CHD events due to elevated risk factors:*

The authors estimate that, for ages 35-74, over a 10-year period, nearly 4.7 million white men and over 1 million white women in the US with elevated risk factors will experience a first MI or cardiac death.

A significant number of events will also occur in younger persons.

More than 90% of CHD events will occur in persons with 1 or more elevated risk factors. About 8% of MI and cardiac deaths will occur in individuals with multiple borderline risk factors (without a single elevated risk factor).

More than 25% of CHD events will occur in persons with only a single elevated risk factor.

More than 66% will occur in people with 2 or more elevated risk factors.

DISCUSSION

1. *No borderline or elevated risk factors:*

An optimal CHD risk factor profile is rare among US adults. Individuals in this category experience very few CHD events.

2. *Borderline risk factors:*

Isolated borderline risk factors without any elevated risk factors account for only about 10% of the burden of myocardial infarction and cardiac death over 10 years. The authors comment that the event rate in subjects with only borderline risk factors may be greater over a longer time (eg, 20 or 30 years.).

Borderline risk factors contributed incrementally to risk in the presence of other elevated risk factors.

The study weighted each of the borderline risk factors equally. This may not be appropriate.

A focus on borderline risk factors by drug therapy would seem misplaced in persons without previous

CHD events. Lifestyle measures to reduce borderline levels of risk factors may be more appropriate.

Although clinical trial data indicate that lowering levels of borderline risk factors can improve outcomes, the number needed to treat to prevent one event may be high.

3. *Elevated risk factors:*

Most CHD events were noted in persons with one or more elevated risk factors.

For women age 35-72 the 10-year absolute CHD event rates do not cross the 10% threshold (which is regarded as high) even when 2 risk factors are elevated.

“Overall, our data support the current practice of assessing CHD risk by measuring several risk factors and using an appropriately calibrated risk prediction algorithm to guide intervention.”

The data are also consistent with current national guidelines noting that absolute CHD event rates are lower than 10% over 10 years in individuals with 0 or 1 elevated risk factors.

4. *Age:*

Nearly 15% of myocardial infarctions and cardiac deaths in men occurred prematurely (before age 55).

In men, one sixth of CHD events occur before age 55. and one tenth occur in women under age 55.

As the population ages, the incidence of atherosclerotic events increases in women and eventually surpasses that in men.

5. *Public health implications:*

About 1/6 of CHD events in men and 1/10 of CHD events in women occur before age 55. (*Efforts should be made to identify elevated major risk factors long before middle age and to intervene appropriately.*)

“Our data indicate that about 2/3 of men and 1/3 of women age 35 to 44 have an elevated modifiable risk factor that could be targeted for intervention.”

Isolated borderline risk factors account for only about 1/10 the burden of acute myocardial infarction and cardiac death. (*Still, 10% of 6 million is about 600 000 events over ten years. RTJ*) Non-pharmacologic measures to reduce borderline risk factors may be more appropriate.

“Overall, our data support the current practice of assessing CHD risk by measuring several risk factors and using an appropriately calibrated risk prediction algorithm to guide interventions.”

The data are also consistent with current national guidelines noting that absolute CHD event rates over 10 years are lower than 10% in individuals with 0 to 1 elevated risk factor.

CONCLUSION

The great majority of Americans have elevated risk factors for cardiovascular disease.

Borderline CHD risk factors alone account for a small proportion of CHD events over a 10-year period.

Annals Int Med March 15, 2005; 142: 393-402 Original investigation, first author Ramachandran S Vasan, Framingham Heart Study, Framingham, Mass.

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Risk Is Lowered Continuously As The Risk Factor Is Lowered.

3-2 THE MIDDLE-AGED AND OLDER AMERICANS; Wrong Prototype for A Preventive Polypill?

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

Most Americans older than age 55 have one or more risk factors for cardiovascular disease” 1/3 or more have hypercholesterolemia, 1/5 smoke, most have inactive lifestyles, 1/3 have high BP. About 1/3 are obese, about 1/10 have diabetes.

Americans have a dizzying array of options to reduce risk. Preventive approaches aimed primarily at identifying and treating individual risk factors were popular in the 1980s and 1990s but had limited success. Social and environmental changes curbed some factors such as smoking, but increased obesity and sedentary lifestyles. Treatment recommendations that targeted single risk factors were incomplete and contained discrepancies from guidelines targeting other risk factors. There were no clear treatment thresholds for factors such as BP, lipid levels, abdominal obesity, and physical activity.

Although relative treatment benefits were proved similar for different levels of certain risk factors, absolute benefits were greatest with treatment for higher-risk persons.

Optimal assessment of absolute risk requires knowledge of multiple risk factors.

Recognizing these issues, experts now recommend assessment of an individual’s *global* risk for vascular disease when deciding whether to treat risk factors, and when selecting specific target levels for those risk factors. For example, recent recommended treatment thresholds and target levels for low-density cholesterol (LDL) vary depending on whether individuals have low, high, or very high risk for coronary heart disease.

Both the single risk-factor based and the global risk-factor-based approaches rely on measurement of the individual’s risk factors.

In 2003 Wald and Law¹ proposed a radical population-based strategy that they claimed would reduce cardiovascular disease by 80%, and have greater impact on public health than any other preventive strategy. They advised discarding the view that risk factors need to be measured and treated individually if found to be ‘abnormal’. Instead they advocated treating *all* adults older than age 55 with a “Polypill” containing low doses of a statin, folic acid, aspirin, and 3 antihypertension drugs. (Low-dose presumably would be associated with fewer adverse effects. This was based on the premise that risk factors are present in *everyone* in western societies, determination of individuals’ global risk is not necessary, and that 96% of deaths from vascular disease occur in people over age 55. Monitoring each individual’s risk factor level to assess treatment benefits is of limited usefulness.

Risk factor interventions with drugs and lifestyle modifications are effective whatever the initial level of the risk factor.

The editorialists go on: Current guidelines recommend identifying and treating elevated risk factors. Many doctors feel obligated to treat higher levels more intensively than borderline levels. A shotgun approach would probably cause collateral damage from adverse drug events in low-risk people who have little potential to benefit from treatment. The benefits and feasibility of low-dose combination therapies administered regardless of risk factor level are not proven. “We believe that the benefits are probably less and harms are probably greater than those proposed by Wald and Law.”

The editorialists nevertheless welcome development and testing combination pills aimed at treating more than one risk factor simultaneously.

Many risk factors are clear. Americans have them in abundance. Despite this, treating everyone older than age 55 with a low-dose Polypill without measuring risk factors may be too audacious for Americans. Adverse effects will likely occur from these multi-drug pills in low risk patients who have little potential for benefit.

The editorialist nevertheless welcomes development of combination pills aimed at treating more than one risk factor simultaneously.

We should not forget the lifestyle measures which are no-risk and are of great benefit in reducing risk.

Annals Int Med March 15, 2005; 143; 467-68 Editorial, first author Cynthia Mulrow, Deputy Editor, Annals Internal Medicine, Philadelphia, PA

1 “A Strategy to Reduce Cardiovascular Disease by More than 80%” (The Polypill) BMJ 2003;326: 1419

2 See also “Risk Factor Thresholds: Their Existence Under a Scrutiny” BMJ 2002;324: 1570-76

These articles by Wald and Law suggested that risk factors make poor screening tools. They highlight that risk rises *continuously* as the level of the risk factor rises. And lowers continuously as the risk factor is lowered.

The levels below which no further benefit can be obtained are undefined. But certainly individuals with what might be considered a “low-risk level” of risk factors can obtain benefit from lowering them further.

The population-attributable risk associated with a certain level (borderline or elevated) of a risk factor depends not only on its relative risk, but also on the prevalence of the risk factor in the population. Since risk factors are universally present in the population, they recommend treatment of *everyone* over age 55.

The object is not to “normalize” risk factors, but to reduce all of them as much as reasonably possible.

A given change in the variables reduces the risk of disease by a constant proportion of the existing risk irrespective of the starting level of the variable. Certain key dose-response relations have no threshold and yield straight lines when risk of disease is plotted on a logarithmic scale. Irrespective of the level of a risk factor, a given change results in the same proportional reduction in risk regardless of the initial risk .

Terms like hypertension and hypercholesterolemia, that focus medical attention on the tails of the distributions of physiological variables are best avoided. The lower the risk factor (down to levels well below average) the lower the risk of disease. Average Western values should not be regarded as normal.

“Blood pressure lowering drugs should not be limited to people with high BP, nor cholesterol lowering drugs to people with high serum cholesterol levels. The constant proportional relation means that there is value in modifying risk factors regardless of the level of the risk factor.”

Offering preventive treatment only to people with relatively high values of a variable means that only a small proportion of those destined to have disease events will be targeted. People at a given age with relatively high values of the physiological variables are at similar risk as people a few years older with average levels. Present practice is illogical in offering preventive treatment to the former, but not to the latter.

Because there are substantial benefits from lowering variables from any starting value, all the reversible risk factors should be changed, not just those judged “abnormal”.

The goal should not be to “normalize” risk factors, but simply to reduce them as much as possible with safety and low cost.

A Practical Definition Of Hypertension: The Value Of BP Below Which No Further Benefit Of Lowering The BP Can Be Demonstrated

3-3 HYPERTENSION—TIME TO MOVE ON

Over the past few decades, guidelines for the treatment of hypertension have progressively been redefined. A larger and larger proportion of the population has been gradually encompassed.

Today, between a fifth and a quarter of most adult populations would meet the definition of “hypertension”. The JNC-7 has recently gone a step further and created a new class—“prehypertension”.

In view of the *continuous* associations between BP and cardiovascular disease risks, the value of categorical systems for classifying BP is questionable. Such categorical systems provide little useful information about an *individual's* risk of actually developing a blood-pressure-related cardiovascular disease. Most guidelines acknowledge that risks are determined by many factors and not by BP alone. This multiplicity of disease determinants is not usually noted in criteria used for the diagnosis or classification of hypertension.

A practical definition of hypertension is the value of BP below which no further benefit of lowering the BP can be demonstrated. There is now compelling epidemiological evidence of *continuous* associations between usual BP values down to about 115/75 and risks of major cardiovascular disease. Non-hypertensive individuals with multiple risk factors or a history of cardiovascular disease will often be at higher *absolute* risk of BP-related cardiovascular events than hypertensive patients without other risk factors.

The population burden of diseases related to BP in non-hypertensive patients is generally greater than that in hypertensives.

Clear evidence now shows that BP-lowering drugs reduce the risk of major vascular events in a broad range of non-hypertensive individuals with high-risk disorders such as cerebrovascular disease, diabetes and coronary heart disease. The absolute benefits of BP-lowering for such patients (irrespective of their initial BP) are substantially greater than those seen in patients with uncomplicated hypertension.

“So why do we persist with this focus on the treatment of hypertension (defined arbitrarily) rather than the prevention of blood-pressure-related diseases?”

Lancet March 19, 2005; 365: 1108-09 “Viewpoint”, editorial, first author S MacMahon, University of Sydney, Australia.

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The Combination Achieved Better Analgesia At Lower Doses Of Each Drug Than Either Given Alone

3-4 MORPHINE, GABAPENTIN, OR THEIR COMBINATION FOR NEUROPATHIC PAIN

The available drugs for neuropathic pain (NP) are incompletely effective and have dose-limiting adverse effects.

This study assessed the effectiveness of a combination of morphine + gabapentin vs either alone and placebo for pain due to diabetic neuropathy and post-herpes zoster neuralgia.

Conclusion: The combination achieved better analgesia at lower doses than either used alone.

STUDY

1. Randomized, double-blind, active placebo-controlled crossover trial of 57 patients (35 with diabetic neuropathy and 22 with post-herpetic neuralgia).
2. Randomized sequentially in 4 periods each given for 5 weeks separated by 4 days washout:
Drugs were given 3 times daily in random sequence:
 - 1) Lorazepam (*Atenolol*; a benzodiazepine) 0.1 to 0.2 mg as an active placebo.
 - 2) Morphine alone (oral sustained-released capsules 15 or 30 mg) Ceiling dose = 120 mg.
 - 3) Gabapentin (*Neurontin*) alone 300 or 400 mg. Ceiling dose = 3200 mg.
 - 4) The combination. Ceiling dose 60 mg morphine + 2400 mg gabapentin.
3. Doses were titrated upward to maximum tolerance or to the ceiling.
4. At baseline, patients completed a diary which rated intensity of their pain 3 times daily after discontinuing all previous medication. They kept a similar diary during the study.
5. Outcome measurer = intensity of pain on a scale of 0 to 10, and on the McGill Pain Questionnaire on a scale of 0 to 45.

RESULTS

1. 41 patients completed the trial.
 2. On a scale of 1 to 10
- | | Baseline | Placebo | Gabapentin | Morphine | Morphine + gabapentin |
|------------------------|----------|---------|------------|----------|-----------------------|
| Mean daily pain scores | 5.7 | 4.5 | 4.2 | 3.7 | 3.06 |
3. McGill Pain Questionnaire
- | | | | | | |
|-----------------------|------|------|------|------|-----|
| On a scale of 0 to 45 | 18.9 | 14.4 | 10.7 | 10.7 | 7.5 |
|-----------------------|------|------|------|------|-----|
4. Doses of morphine and gabapentin were lower with the combination than for each given separately.
 5. Main adverse effects = constipation, sedation, and dry mouth.

DISCUSSION

1. Treatment with a combination of morphine + gabapentin resulted in greater relief of pain than treatment with either alone.

2. The combination was associated with significantly less pain-related interference with mood, and higher scores for vitality and social functioning. The combination was also associated with improvement in depression as measured by the Beck Depression Inventory.
3. Doses of morphine + gabapentin were significantly lower than in treatment with either alone.
4. The study also confirmed the beneficial effects of morphine when used alone for patients with neuropathic pain.
6. Gabapentin significantly enhanced the efficacy of morphine in patients with diabetic neuropathy and post-herpetic neuralgia.

CONCLUSION

The combination of morphine + gabapentin achieved better analgesia at lower doses of each drug than either given as a single agent.

NEJM March 31, 2005; 352: 1324-34 Original investigation, first author Ian Gilron, Queen's University, Kingston, Ontario, Canada.

Addition of Clopidogrel Improved Patency of The Affected Artery and Reduced Ischemic Complications.

3-5 ADDITION OF CLOPIDOGREL TO ASPIRIN AND FIBRINOLYTIC THERAPY FOR MYOCARDIAL INFARCTION WITH ST-SEGMENT ELEVATION

A substantial proportion of patients receiving fibrinolytic therapy for MI with ST-segment elevation have inadequate reperfusion or re-occlusion of the infarct-related artery. Initial reperfusion fails to occur in about 20% of patients. This is associated with a doubling of mortality rates. The artery becomes re-occluded in another 5% to 8% during the index hospitalization. This further increases mortality.

Platelet activation and aggregation play a key role in initiating and propagating coronary artery thrombosis. In patients with ST-elevation acute MI, aspirin reduces death from vascular causes by 23% and the odds of reinfarction by 46%. It also reduces rate of angiographic re-occlusion by 22%.

Clopidogrel (*Plavix*) acts differently from aspirin in inhibiting activation and aggregation of platelets. It reduces rate of death and ischemic complications in patients with symptomatic atherosclerotic disease, in patients who have undergone PTCA, and in patients with unstable angina and non-ST-segment elevation MI.

This study asks: Does addition of clopidogrel benefit patients with acute ST-segment elevation MI who are receiving fibrinolysis and aspirin?

Conclusion: Addition of clopidogrel improved patency of the affected artery and reduced ischemic complications.

STUDY

1. Enrolled over 3400 patients (mean age 57) who presented within 12 hours after onset of an ST-segment elevation MI. Essentially all were treated with aspirin, fibrinolytic therapy (within a median of 2.5 hours), and received heparin for 48 hours. The great majority also received a statin drug, a beta-blocker, and an ACE inhibitor.
2. Randomized to: 1) clopidogrel (300 mg loading dose followed by 75 mg once daily), or 2) placebo.
3. Patients were to receive study medication daily up to and including the day of coronary angiography.
For patients who did not undergo angiography, the study drug was to be administered up to and including day 8 or hospital discharge. (*This was a short-time study. RTJ*)
4. Almost all received angiography at a median of 3.5 days.
5. Primary efficacy endpoint = composite of an occluded infarct-related artery on angiography, or death, or recurrent MI before angiography.

RESULTS

- | 1. | Placebo (%) | Clopidogrel (%) | Absolute difference (%) | NNT |
|---------------------------|-------------|-----------------|-------------------------|-----|
| Primary efficacy endpoint | 21.7 | 15.0 | 6.7 | 15 |
| At 30 days | 11.6 | 14.1 | 2.5 | 40 |
2. Rates of bleeding and intracranial hemorrhage were similar.

DISCUSSION

1. “Our study demonstrates the benefit of adding clopidogrel to aspirin and fibrinolytic therapy of MI with ST-segment elevation.” The benefit was consistent across a broad range of subgroups.
2. Treatment was not associated with an increased rate of major bleeding or intracranial hemorrhage.
3. Clopidogrel is a potent anti-platelet agent that has a synergistic antithrombotic effect when combined with aspirin.
4. The authors mention that newer fibrinolytic agents (tenecteplase, reteplase) are equivalent but not superior to older fibrin-specific agents (alteplase, streptokinase). All four were used in the study.

CONCLUSION

In patients younger than age 76 who have an acute ST-segment elevation MI, who received aspirin and a standard fibrinolytic regimen, the addition of clopidogrel improved patency rate of the infarct-related artery, and reduced ischemic complications.

NEJM March 24, 2005; 352: 1179-89 Original investigation, first author Marc S Sabatine, Brigham and Women’s Hospital and Harvard Medical School, Boston, Mass.

“Concurrent Antiplatelet and Fibrinolytic Therapy”, an editorial in this issue of NEJM (pp 1248-50) comments and expands on the study:

Aspirin is a relatively weak antiplatelet agent. It has limitations. It irreversibly inhibits cyclo-oxygenase in platelets thereby inhibiting synthesis of thromboxane, a powerful promoter of platelet activation. It exerts no effect on

thromboxane-independent mediators of platelet activation. Up to 30% of persons with coronary artery disease are relatively resistant or unresponsive to aspirin.

All mediators of platelet activation cause conformational changes in the platelet-surface glycoprotein IIb/IIIa receptor. This change retards platelets from binding to circulating fibrinogen.

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Reduced Ischemic Stroke, but Did Not Reduce MI, Except in Women Over Age 65

3-6 RANDOMIZED TRIAL OF LOW-DOSE ASPIRIN IN THE PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE IN WOMEN.

Cardiovascular disease is the leading cause of death among both women and men.

Aspirin is effective in *treatment* of acute myocardial infarction and in *secondary* prevention of cardiovascular disease among both men and women.

Its use in *primary* prevention in women is controversial. The current recommendations for use of aspirin in *primary* prevention in women are based on limited data.

The Women's Health Study was a large, randomized, double-blind placebo-controlled trial of low-dose aspirin in the primary prevention of cardiovascular disease among over 39 000 apparently healthy women followed for a mean of 10 years for major cardiovascular events.

Conclusion: In primary prevention, aspirin lowered risk of stroke in women over age 45; but did not lower risk of myocardial infarction or cardiovascular death until after age 65.

STUDY

1. Entered over 38 000 women age 45 or older (mean = 54) . All were initially healthy. 10% were over age 65.
2. Randomized to: 1) Aspirin 100 mg daily on alternate days, or 2) Placebo
3. Followed for 10 years to determine first major cardiovascular event (non-fatal MI, non-fatal stroke, or death from cardiovascular causes.

RESULTS

1. During 10-year follow-up:

A. Entire group	Aspirin (n = 19 934)	Placebo (n = 19 942)
Major cardiovascular events	477	522*
Stroke		
Ischemic	221	266
Hemorrhagic	51	41*
Fatal	23	22*
Non-fatal	198	244
Myocardial infarction		
Fatal	14	12*
Non-fatal	184	181*
Death from CV disease	120	126*

Transient ischemic attack	186	238
Bleeding requiring transfusion	127	91

(* Not statistically significant for the entire group. Note the large numbers of subjects in both arms of the study. By my calculation 900 individuals would need to be treated for 10 years to prevent one ischemic stroke. Is this clinically significant?—especially when the increased risk of hemorrhages is considered. RTJ)

B. Group over age 65 (n = 4000)	Aspirin	Placebo
Major cardiovascular event	131	175
Ischemic stroke	53	75
Myocardial infarction	41	62

(All results in this older group were significant. By my calculation 500 individuals would need to be treated for 10 years to prevent one ischemic stroke. Is this clinically significant?—especially when the increased risk of hemorrhages is considered. RTJ)

2. Gastrointestinal hemorrhage requiring transfusion more frequent in the aspirin group.

(Relative risk =1.4)

DISCUSSION

1. Over the entire group of 39 000 women, primary prevention with aspirin was associated with a non significant reduction in risk of major cardiovascular events, a slightly reduced risk of TIA, total stroke, and ischemic stroke, And no significant effect on risk of myocardial infarction or death from cardiovascular causes.
2. Subgroup analysis showed that aspirin was associated with a statistically significant reduction in major cardiovascular events, ischemic stroke, and myocardial infarction *among women age 65 and older at baseline.*
3. As expected, the frequency of bleeding and stomach ulcers was greater in the aspirin group. (RR = 1.40)
4. Other trials of secondary prevention, however, have reported clearly reduced risk of cardiovascular events, myocardial infarction and ischemic stroke in women as well as men.

CONCLUSION

Prophylactic aspirin lowered risk of stroke in women over age 45; did not lower risk of myocardial infarction or death from cardiovascular causes except in women over age 65. Use was associated with a higher risk of GI bleeding.

NEJM March 31, 2005; 352: 1293-304 Original investigation , first author Paul M Ridker, Brigham and Women's Hospital, Boston, Mass.

Warfarin Provided No Benefit Over Aspirin. It Was Associated With Higher Rates Of Adverse Events.

3-7 COMPARISON OF WARFARIN AND ASPIRIN FOR SYMPTOMATIC INTRACRANIAL STENOSIS.

Atherosclerotic stenosis of the arteries within the cranium is an important cause of stroke. The risk of recurrent stroke is as high as 15% a year.

Warfarin is commonly used for treatment in preference to aspirin, but the drugs have not been compared in a randomized trial. Retrospective studies have suggested that warfarin is superior. Recently a study comparing the drugs in non-embolic stroke (mostly lacunar infarcts) reported similar rates of recurrent stroke.

Neurologists in the US are evenly divided between recommending warfarin and aspirin.

This randomized trial compared the 2 drugs in patients with stenosis of a major intracranial artery.

Conclusion: Warfarin provided no benefit over aspirin. It was associated with significantly higher rates of adverse events.

STUDY

1. Randomized, double-blind multicenter (59 sites) trial entered over 550 patients (mean age 63). All had experienced a TIA or a non-disabling stroke caused by angiographically verified 50% to 99% stenosis of a major intracranial artery (internal carotid, middle cerebral, vertebral, or basilar). Defined ischemic stroke as a new (within the past 90 days) focal neurological deficit of sudden onset that lasted at least 24 hours and was not associated with hemorrhage.
2. No patient had co-existing 50% to 99% stenosis of an extracranial artery or a cardiac source of embolism.
3. Mean BP = 140/77. The authors did not comment on the relatively low BP at baseline other than to state 85% of the subjects had a history of hypertension. (*I presume almost all were receiving therapy. RTJ*)
4. Randomized to: 1) warfarin—target INR of 2.0 to 3.0, or 2) aspirin 650 mg twice daily.
5. Primary endpoint = recurrent ischemic stroke, brain hemorrhage, or death from vascular causes other than stroke.
5. Follow-up planned for 3 years; actual = 1.8 years. The study was terminated early because of concerns about safety of patients who received warfarin.

RESULTS

- | 1. Outcomes: | Death (%) | Major hemorrhage (%) | Death from vascular causes (%) |
|--------------|-----------|----------------------|--------------------------------|
| Warfarin | 9.7% | 8.3 | 5.9 |
| Aspirin | 4.3% | 3.2 | 3.2 |
2. Myocardial infarct occurred in 2.9% of the aspirin group vs 7.3% of the warfarin group.
 3. In the warfarin group INR was less than 2.0 23% of the time; 2.0 to 3.0 63% of the time; and over 3.0 13% of the time.
 4. Study drugs were stopped in 28% of those taking warfarin vs 17% in those taking aspirin.
 5. Primary outcomes about equal—22% vs 22%.

DISCUSSION

1. A post-hoc analysis showed that INR below 2.0 was associated with a significantly higher risk of recurrent ischemic stroke and major cardiac events; an INR above 3.0 was associated with a higher risk of major hemorrhage.

2. The practice of using warfarin rather than aspirin for symptomatic intracranial stroke is not supported by this study. Warfarin was not associated with any outcome advantage over aspirin and was associated with significantly higher major adverse effects.
3. The high dose of aspirin was chosen in part because higher doses decrease platelet resistance, diminish shear-induced platelet aggregation, and may decrease the inflammatory component of atherothrombosis.
4. The narrow therapeutic range of warfarin (INR 2.0 to 3.0) is difficult to maintain in clinical practice. The advent of home monitoring may lessen the difficulty.
5. Important implications for practice: aspirin, rather than warfarin should be used to treat intracranial arterial stenosis; use of aspirin will substantially reduce risk of major hemorrhage and eliminate the inconvenience of use of warfarin.

CONCLUSION

Warfarin provided no benefit over aspirin. It was associated with significantly higher rates of adverse events. "Aspirin should be used in preference to warfarin for patients with intracranial arterial stenosis."

NEJM March 31, 2005; 352: 1305-16 Original investigation by the Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators, first author Marc I Chimowitz, Emory University, Atlanta GA.

An editorial in this issue by Walter J Koroshetz, Massachusetts General Hospital, Boston comments:

Symptomatic intracranial atherosclerotic disease is an extremely aggressive disease. Within 2 years almost a quarter of patients will suffer vascular events regardless of treatment with warfarin or aspirin.

The INRs at the time of adverse events suggest that anticoagulation will benefit if the dose could be strictly regulated. New anticoagulants in the offing may bring much better outcomes.

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Vitamin D Deficiency May Increase Falls in Elderly People

3-8 RECENT DEVELOPMENTS IN VITAMIN D DEFICIENCY AND MUSCLE WEAKNESS AMONG ELDERLY PEOPLE.

The liability of the elderly to fall and sustain fractures is increased by many factors: visual impairment; neurological disorders; orthopedic disabilities; and drug effects.

One study reported that "More than a third of people aged over 65 fall each year." Risk doubles at age 85. A main risk factor is muscle weakness.

Vitamin D deficiency is common in the elderly (especially in the house-bound and nursing home patients). Its prevalence is much greater than previously realized. It may be associated with poor muscle strength as well as osteomalacia.

This review discusses recent developments in screening and treating vitamin D deficiency among the elderly aimed at reducing the incidence of falls and fractures. Deficiency is associated with falls and fractures among the elderly that are not explained by bone density.

Higher plasma levels of calcidiol are associated with muscle strength, physical activity, and ability to climb stairs. Lower levels of calcidiol are associated with falls among the elderly. A randomized trial reported a 47% reduction in falls and fractures in elderly women given 800 IU of vitamin D daily (compared with controls receiving calcium alone) over 12 months.

If vitamin D deficiency is associated with weakness and falls, why does supplementation with vitamin D sometimes fail to help? The author states that supplementation is often inadequate. 400 IU daily may be ineffective. In contrast, 800 IU has been shown to significantly reduce the risk.

Is vitamin D (usually given as cholecalciferol) safe? One study reported that the lowest serum level at which an adverse effect occurred was a calcidiol level of 200 nmol/L. This corresponds to a daily intake of 40 000 IU of cholecalciferol—a 50-fold margin of safety. In a large clinical trial, no adverse effects were observed at a daily dose of 800 IU of cholecalciferol.

Conclusion: Vitamin D deficiency among elderly people is much more common than previously recognized, especially in individuals in nursing homes and those in the community who are housebound.

The consequences include muscle weakness, body sway, and a tendency to falls and fractures.

Treatment with a supplement of 800 IU daily should be seriously considered.

The question of whether to treat all elderly people in the community is problematic. Two thirds are not vitamin D deficient. (250 would need to be treated for a year to prevent one fracture.) The NNT would be lower if treatment were restricted to those over age 80. Treating women with known deficiency would reduce the NNT to 5.

BMJ March 5, 2005; 330: 524-26 “Clinical Review” by Geoff Venning, consultant in pharmaceutical medicine, High Wycombe, UK

Folate and B12 Supplementation May Prevent Some Fractures.

3-9 HOMOCYSTEINE AND FRACTURE PREVENTION

Epidemiological studies suggest that an elevated circulating homocysteine level may be a risk factor for osteoporotic fractures. However, a causal relationship has not been established.

This issue of JAMA presents evidence that an elevated homocysteine level might be associated with brittle bones. The randomized trial¹ of Japanese patients who had suffered hemiplegia due to stroke compared a group given folate and B12 (effectively lowering homocysteine levels) with a control group. The untreated group had 5 times the fracture rate as the treated group.

The fall frequency was similar in both groups. (Ie, with the same frequency of falls, the placebo group had more fractures.)

Vitamin B12 deficiency is common in the elderly. B12 has been linked by a limited number of studies to bone health. Patients with pernicious anemia have a higher risk of fracture. Recent population-based studies suggest that B12 is important for maintaining bone mineral density.

JAMA March 2, 2005; 293: 1121-22 Editorial, first author Joyce B J van Meurs, Erasmus Medical Center, Rotterdam, Netherlands.

1 “Effect of Folate and Mecobalamin (Vitamin B12) on Hip Fracture in Patients with Stroke” JAMA March 2, 2005; 293: First author Yoshihiro Sato, Mitate Hospital, Tagawa, Japan

Double-blind randomized trial followed over 550 elderly patients. All had hemiplegia due to ischemic stroke. Randomized to daily 1) 5 mg folate and 1500 ug of B12, or 2) placebo. Followed up for 2 years to determine incidence of hip fractures.

At baseline, patients had low levels of serum B12 and folate, and high levels of homocysteine. In the treatment group serum homocysteine fell by 38%; increased by 31% in the placebo group. Serum B12 and folate levels increased in the treatment group; fell in the placebo group.

Ten hip fractures occurred in the treatment group vs 43 in the placebo group. The adjusted relative risk was 0.20; absolute risk reduction = 7%; NNT for 2 years to prevent one fracture = 14. The results were similar for all fractures.

No difference in prevalence of falls between groups. No significant adverse effects of folate and B12 were observed.

Bone mineral density was not different between groups. The difference in incidence of fracture occurred despite this lack of difference. The authors suggest that the main risk factor is impaired cross linkage of collagen fibers which may increase bone fragility and which may not be evident on BMD.

“No Compelling Evidence That Higher Doses of Vitamin E Reduce Cardiovascular Risk or Cancer”

3-10 IS THERE ANY HOPE FOR VITAMIN E?

During the past 15 years, epidemiologic, biological, and experimental studies have supported the hypothesis that antioxidants protect against atherosclerosis. The mechanism was presumed to be the inhibition of cholesterol accumulation in endothelial plaques.

Biological mechanisms have also suggested that carcinogenesis may be blocked by antioxidants.

Over the past 3 to 6 years, placebo controlled trials have consistently shown that commonly used antioxidant vitamins (E, C, and beta carotene, or a combination) do *not* significantly reduce overall cardiovascular events or cancer.

This editorial comments on a study in this issue of JAMA¹ which reports a 7-year follow-up on a trial of vitamin E (daily 400 IU of alpha-tocopherol—a natural source). The study was based on a cohort of patients age 50 to 75 who had established cardiovascular disease or diabetes. There was no statistical benefit from the vitamins in reducing risk of total cancer incidence or cardiovascular events.

A subgroup finding reported a possible *harmful* effect—an increased risk of heart failure associated with vitamin E.

“This report effectively closes the door on the prospect of a major protective effect of long-term exposure to this supplement, taken in moderately high dosage, against complications of atherosclerosis and overall cancer incidence.”

This study reemphasizes the importance of controlled trials for testing important hypotheses derived from epidemiological or biological data. The latter can mislead; well-designed clinical trials rarely do.

Conclusion: “In nearly 60 000 patients studied to date, there is no compelling evidence that higher doses of vitamin E reduce cardiovascular risk or cancer”. Indeed, there is a hint that the antioxidant may increase risk of heart failure.

JAMA March 16, 2005; 293: 1387-90 Editorial, first author B Greg Brown, University of Washington School of Medicine, Seattle

1 “Effects of Long-term Vitamin E Supplementation on Cardiovascular Events and Cancer” by the Heart Outcomes Prevention Evaluation (HOPE) Trial

The investigators conclude that...“in conjunction with its lack of efficacy, the potential of harm suggested by our findings strongly supports the view that vitamin E supplements should not be used in patients with vascular disease or diabetes.”