

PRACTICAL POINTERS
FOR
PRIMARY CARE MEDICINE
ABSTRACTED MONTHLY FROM THE JOURNALS
A Free Public-Service Publication

MAY 2009

**USE OF BLOOD PRESSURE LOWERING DRUGS IN THE PREVENTION OF
CARDIOVASCULAR DISEASE: A Meta-analysis and Comments on the "Polypill" [5-1]**

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PERIPHERAL VASCULAR DISEASE [5-4]**

**JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE
www.practicalpointers.org**

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This document is divided into two parts

1) The **HIGHLIGHTS AND EDITORIAL COMMENTS SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

***EDITORIAL COMMENTS** are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 20-year publication of *Practical Pointers*.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 6 years can be accessed at www.practicalpointers.org

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HIGHLIGHTS AND EDITORIAL COMMENTS MAY 2009

A New Approach To Treatment Of Blood Pressure ?

5-1 USE OF BLOOD PRESSURE LOWERING DRUGS IN THE PREVENTION OF CARDIOVASCULAR DISEASE: A Meta-Analysis Of 147 Randomised Trials In The Context Of Expectations From Prospective Epidemiological Studies.

Despite the widespread use of BP-lowering drugs and the results from many randomized trials, uncertainty remains about which drugs to use, and who to treat.

Five questions encapsulate the uncertainty:

1. Do beta-blockers have a special effect over and above lowering BP in preventing coronary heart disease (CHD) events in people with a history of CHD?

Yes. The effect is an approximate 30% reduction in CHD, present for a few years after the infarct. This risk reduction is about 15% thereafter, similar to that of other BP lowering drugs.

2. Does the effect of BP-lowering drugs in preventing CHD and stroke differ in people with and without a history of cardiovascular disease? (Ie, is there a different effect in secondary and primary prevention?)

No. The percentage reduction in risk of CHD events and stroke is the same or similar. Since the absolute risk is highest in people with a history of cardiovascular disease, the absolute risk reduction is greater.

3. Does BP reduction alone explain the effect of BP-lowering drugs in preventing CHD and stroke?

Yes, except for the special short term effect of beta-blockers.

4. Should the use of BP-lowering drugs be limited to people with “high” BP ?

No. BP lowering drugs should be offered to anyone with a high enough risk to benefit from treatments whatever the reason for being at high risk, because a given blood pressure reduction lowers risk of CHD and stroke by a constant relative (*but not absolute*) proportion irrespective of pretreatment blood pressure.

5. What is the quantitative effect of taking one or more BP-lowering drugs in lowering BP and preventing CHD events and stroke according to dose, pretreatment BP, and age?

In people age 60-69, with a diastolic of 90 or systolic of 150, one drug at standard dose lowers the risk of CHD by about 25%, and of stroke by about 35%. Three drugs at half standard dose lower the risk of CHD by about 45% and of stroke by about 60%. The estimates are about 10 percentage points higher if blood pressure is higher by 30/15.

The estimates are about 5 percentage points lower for a 10 year increase in age.

These investigators answered these questions using the results of 147 randomized trials of BP-lowering drugs and CHD events (n = 22 000) and stroke (n = 12 000), and correlated their results with several large previously published meta-analyses. They also quantified the effect of BP-lowering drugs on the incidence of heart failure, cancer mortality, and other non-vascular mortality, and all-cause mortality.

This is a large, complex meta-analysis. The abstract is by far the longest I have ever written. And the most difficult.

I believe its length is justified by its importance to primary care. The authors present some novel and, I believe, controversial arguments about lowering BP, some of which would represent a sea-change in our approach to treatment of blood pressure.

Please read the full abstract.

What change from our present approach does this study suggest? Should we change our approach? How would I respond to their suggestions?

- 1. The study is based on relative risk reductions. To apply to primary care patients we must rely on absolute risk reductions in individuals as related to age and past history of CHD and stroke and other factors.*
- 2. Response to antihypertension therapy will vary from patient to patient. Individualization is required.*
- 3. The observation that all 5 drugs are equally effective in lowering BP will enable freer choice according to patients' response and preference.*
- 4. Early on, I would prescribe a combination of low dose drugs. There is strong evidence that a combination of 2 or 3 drugs at low dose is more effective than one drug at higher dose, and the combination is safer.*
- 5. I would be more aggressive in lowering BP in patients at higher risk because of age or past history. This would extend to those with a BP well below the cut point of 140/90.*
- 6. BP is not the only risk factor to reduce. Lowering other risk factors will modify the effect of lowering BP.*
- 7. Patients should be followed for effectiveness and adverse effects. Individual patients will vary.*
- 8. I would be more willing to cautiously prescribe beta-blockers for patients with heart failure and post-myocardial infarction*

5-2 EFFECT OF CLOPIDOGREL ADDED TO ASPIRIN IN PATIENTS WITH ATRIAL FIBRILLATION

This study assessed whether clopidogrel + aspirin would reduce risk of thromboembolic stroke and other major vascular events in patients with AF to a greater degree than aspirin alone. And whether clopidogrel + aspirin would lead to greater risk of hemorrhage.

A double-blind, randomized trial in 580 centers in 53 countries followed over 7500 patients with AF (mean age 71). All subjects had AF at entry or had at least two episodes of AF in the past 6 months. They were considered “unsuitable” for warfarin therapy.

Randomized to: 1) aspirin (75-100 mg daily) + placebo (**aspirin-alone**), or 2) clopidogrel (*Plavix*; Bristol Myers Squibb; 75 mg daily) + aspirin. (**C + A**)

Primary outcome = combination of stroke, myocardial infarction, non-CNS systemic embolization, or death from vascular causes.

Outcomes (% per year)	C + A	Aspirin-alone	Absolute difference	NNT
Primary outcome	6.8	7.6	0.8	125
Ischemic stroke	1.9	2.8	0.9	111
Hemorrhagic stroke	0.2	0.2	--	
Disabling or fatal stroke	1.6	2.1	0.5	200
Risks of hemorrhage (%/y):				NNH
Major bleeding	2.0	1.3	0.7	143
Minor bleeding	3.5	1.4	2.1	47
Intracranial bleeding	0.4	0.2	0.2	500

The addition of clopidogrel to aspirin (as compared with aspirin alone) reduced the rate of major vascular events from 7.6% per year to 6.8% per year, primarily due to a reduction in stroke. (*NNT for one year to prevent one major vascular event = 125; to prevent one stroke = 111. One in 143 will experience a major hemorrhage.*)

“It is important to emphasize that oral anticoagulation with a vitamin K antagonist is the preferred and recommended therapy for the prevention of ischemic stroke in patients with atrial fibrillation.”

Use of C + A did not result in a significant reduction in mortality from any cause. The majority of deaths in this study were due to arrhythmia, heart failure, and non-vascular causes.

Conclusion: In patients with AF for whom warfarin therapy was “unsuitable”, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage.

Plavix is widely advertised directly to the public. It is expensive. My drug store quotes a price of \$4.77 for one 75 mg tablet. To reduce the occurrence of one major vascular event over 1 year, 125 patients must be treated with C + A vs aspirin-alone; 124 will take the drug without benefit. Each will be exposed to adverse effects and a cost of \$1,741.00 yearly.

The yearly cost of prescribing Plavix to the 124 patients (and to society) who will not benefit will be \$215,884.00. Caring for the additional patients who have major bleeding when taking Plavix adds to the cost.

The benefit / harm –cost ratio of Plavix is very low.

Whether to use warfarin, clopidogrel, aspirin, or a combination of clopidogrel + aspirin in patients with AF is a high-risk decision. Patients must be fully informed about benefits, adverse effects, and cost before making their personal judgment.

Primary care clinicians are in a no-win situation when prescribing anticoagulants and anti-platelet drugs for AF. If the patient does not experience a thromboembolic stroke, there is no way of determining whether the drug prevented it. If the patient experiences a major bleeding episode, the physician will blame herself, and the patient will blame the physician and the drug.

Should Be Used for Secondary Prevention. Use for Primary Prevention Is Debatable.

5-3 ASPIRIN IN THE PRIMARY AND SECONDARY PREVENTION OF VASCULAR DISEASE

A Collaborative Meta-Analysis Of Individual Participant Data From Randomised Trials

Long-term, low-dose aspirin is of definite and substantial benefit for many people who already have occlusive vascular disease and are at high risk for recurrence. (Secondary prevention)

For secondary prevention, benefit of aspirin substantially exceeds the risk of bleeding.

For primary prevention, the balance is less clear. The absolute benefits in primary prevention are generally on order of magnitude lower than in secondary prevention.

Current guidelines largely ignore any differences in bleeding risk and recommend that aspirin be used widely for primary prevention in those at moderately raised risk for coronary heart disease (CHD).

In this meta-analysis, primary prevention trials were eligible only if they involved a randomized comparison of aspirin vs no aspirin. Persons with any history of occlusive vascular disease and diabetes were excluded. Six primary prevention trials (95 000 persons) were included.

Secondary preventions trials included individuals with previous myocardial infarction, stroke, or transient ischemic attack (16 trials; 17 000 persons) that compared long-term aspirin vs controls.

Yearly absolute difference (% per year aspirin vs control):

	Primary prevention	Secondary prevention
Major coronary event	-0.06 %	-1.00 %
Non-fatal MI	-0.05	-0.66
CHD mortality	-0.01	-0.34
Stroke	-0.01	-0.46
Vascular death	-0.01	-0.29
Any serious vascular event	-0.07	-0.29
Major extracranial bleed	+0.07	a

(a. Extracranial bleeding incompletely reported.)

Primary prevention trials: The NNT (number needed to treat to benefit one patient over one year) varied from 1111 to 10 000. The number needed to treat to harm (NNTharm) one primary prevention patient per year (major hemorrhage) = 1428.

Secondary prevention trials: The NNT to benefit one patient per year varied from 100 to 344—about ten times the benefit in primary prevention. (*I assume the bleeding complications (NNTharm) were comparable to those in primary prevention trials. RTJ*)

In the primary prevention trials, the absolute risk of a serious vascular event among people of a given age and sex was an order of magnitude less than in secondary prevention trials.

In primary prevention, the absolute reduction in occlusive events would be only about twice as large as the absolute reduction in bleeding. Moreover, these trials of aspirin were mainly in people who were not taking statin therapy, which would have reduced both myocardial infarction and ischemic stroke with little hazard.

There is still a possibility that there is some particular category of individuals in whom primary prevention with aspirin is of definite benefit. Adults with diabetes may benefit more.

Even in people at moderately increased risk of CHD, the absolute benefits and harms of adding aspirin to a statin-based primary prevention regimen could still be approximately evenly balanced.

Conclusion: For primary prevention in persons without previous vascular disease, aspirin is of uncertain net value. Reductions in occlusive events should be weighed against the increased risk of major bleeding. For secondary prevention, benefits of long-term aspirin outweigh risks.

I recall when the US Physicians' Health Study was published (1988), many persons including many physicians began to take low-dose aspirin daily. Since then, some of the bloom has come off this

application. But many people still take aspirin for primary prevention. And many guidelines advise it for certain groups (eg, diabetes).

Secondary prevention should continue routinely.

The decision for primary prevention is up to the individual patient's preference after full explanation of possible harms and benefits. The chief message of the study was to point out harms as well as benefits. Patients should be so informed.

Other risk factors must be controlled as well: lipids, blood pressure, BMI, smoking, physical fitness with life-style modifications as well as drugs. I would be reluctant to prescribe aspirin to a patient with uncontrolled BP. I believe that aspirin is much less important in primary prevention than control of these risk factors.

I believe that individuals who have never experienced a vascular event may be at almost as great a risk of an event as those who have experienced an event, especially if treatment has reduced risk factors in the latter group.

The Current Evidence Is Insufficient To Rule Out A Small Yet Important Benefit

5- 4 ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE: A Meta-analysis of Randomized Trials

The effect of long-term, low dose aspirin on patients with peripheral artery disease (**PAD**) is uncertain.

Despite the paucity of data, major guidelines support the use of aspirin as first-line therapy for patients with PAD. However, the FDA concluded that there is insufficient evidence to support a labeling indication for aspirin in patients with PAD.

This meta-analysis of patients with PAD evaluated all the available evidence from prospective, randomized trials of aspirin alone or in combination with other antiplatelet drugs in secondary prevention of cardiovascular events. It tested the null hypothesis that aspirin was not different from placebo in reducing risk of the combined primary endpoint of non-fatal MI, non-fatal stroke, and cardiovascular death.

A literature search found 18 prospective, randomized trials of aspirin, with or without dipyridamole (5269 individuals with PAD). Aspirin dose ranged from 100 mg/d to 1500 mg/d for monotherapy, and from 25 mg aspirin + 75 mg dipyridamole to 325 mg aspirin + 75 mg dipyridamole.

Primary endpoint = cardiovascular events (non-fatal MI, non-fatal stroke, and cardiovascular death).

A total of 251 cardiovascular events (the primary endpoint) took place among 2823 patients receiving any aspirin vs 169 among 2446 controls (8.9% vs 11%; 12% reduction). The difference was not statistically significant.

The risk of non-fatal stroke was lower in the aspirin group (1.8% vs 3.1%). This was statistically significant.

Effect of aspirin monotherapy on the primary outcome: 125 cardiovascular events among 1516 patients vs 144 events among 1516 controls (8.2% vs 9.6%; not significant). Aspirin was associated with a significant reduction in non-fatal stroke (2.1% vs 3.4%).

Two trials compared low dose (100 mg) aspirin monotherapy with placebo: 112 cardiovascular events occurred among 823 participants vs 127 events among 819 placebo participants (13.6% vs 15.5%). Although not statistically significant, the population studied was small, and the 95% confidence interval was wide, potentially limiting detection of important cardioprotective events.

“Results of this meta-analysis demonstrated that, for patients with PAD, aspirin therapy alone or in combination with dipyridamole did not significantly decrease the primary endpoint of cardiovascular events.” This may reflect limited statistical power. Smaller levels of benefit, such as a 20% reduction, cannot be excluded with the available evidence.

Aspirin was associated with a significant reduction of non-fatal stroke.

There was no significant benefit noted for non-fatal MI, cardiovascular mortality or all-cause mortality.

Conclusion: This meta-analysis did not demonstrate a significant benefit of aspirin vs placebo on cardiovascular events in patients with PAD. Aspirin significantly reduced risk of non-fatal stroke.

The current evidence is insufficient to rule out a small yet important benefit.

The NNT with aspirin for one year to benefit one patient could not be calculated from the data in the meta-analysis. It is likely to be very large.

If atherosclerosis is widespread and severe, it may be too much to ask aspirin to benefit. The subjects in this meta-analysis had advanced PAD.

Aspirin is still being highly advertised for primary prevention.

Guidelines continue to recommend aspirin. Many PCPs will continue to use it for primary and secondary prevention.

Diabetes with or without PAD is considered an indication for aspirin prophylaxis.

The significant reduction in non-fatal stroke may be enough to convince some patients to accept aspirin prophylaxis.

How should primary care clinicians now respond to this latest information?

- 1. Aspirin is effective in secondary prevention. It may be effective in primary prevention.*
- 2. If aspirin is used, low doses should be prescribed (75-81 mg/d). Low doses are effective and cause less harm*
- 3. Patients should be made aware of the possible harm of bleeding as well as possible benefits in order to make a personal informed choice for primary prevention. Harms and benefits are roughly equal. Patients may fear the harm of bleeding less than the harm of stroke and MI.*
- 4. Aspirin prophylaxis probably does lower risk of cardiovascular complications. Aspirin cannot approach the effectiveness of controlling other well established risk factors (lipids, BMI, blood pressure, fitness, smoking) in lowering risk.*

ABSTRACTS MAY 2009

A New Approach To Treatment Of Blood Pressure ?

5-1 USE OF BLOOD PRESSURE LOWERING DRUGS IN THE PREVENTION OF CARDIOVASCULAR DISEASE: A Meta-Analysis Of 147 Randomised Trials In The Context Of Expectations From Prospective Epidemiological Studies.

Despite the widespread use of BP-lowering drugs and the results from many randomized trials, uncertainty remains about which drugs to use, and who to treat.

Five questions encapsulate the uncertainty:

Do beta-blockers have a special effect over and above lowering BP in preventing coronary heart disease (**CHD**) events in people with a history of CHD? This view is widely held, but such an effect has not been quantified.

Does the effect of BP-lowering drugs in preventing CHD and stroke differ in people with and without a history of cardiovascular disease? (Ie, is there a different effect in secondary and primary prevention?)

Does BP reduction alone explain the effect of BP-lowering drugs in preventing CHD and stroke? (Is there a so called pleotropic effect of the drugs?) Selected trial data have been used to suggest that each of the 5 main classes of BP-lowering drugs: thiazides, beta-blockers (**BB**), angiotensin converting enzyme inhibitors (**ACE**), angiotensin II receptor blockers (**ATRB**), and calcium channel blockers (**CCB**) has a greater preventive effect. Clinical guidelines reflect the view that differences in efficacy exist.

Should the use of BP-lowering drugs be limited to people with “high” BP, and not given to those at risk of cardiovascular disease who have a lower BP? A corollary is whether BP should be reduced to a limited extent only—a treat to target approach. Cohort (prospective observational) studies do not show a lower BP limit below which risk ceases to decline.

What is the quantitative effect of taking one or more BP-lowering drugs in lowering BP and preventing CHD events and stroke according to dose, pretreatment BP, and age?

These investigators answered these questions using the results of 147 randomized trials of BP-lowering drugs, and CHD events (n = 22 000) and stroke (n = 12 000). They compared the results of their meta-analysis with a large meta-analysis of cohort studies.¹

They also quantified the effect of BP-lowering drugs on the incidence of heart failure (**HF**), cancer mortality, and other non-vascular mortality, and all-cause mortality.

METHODS

A database search identified randomized trials of BP-lowering drugs in which CHD events or stroke were recorded. Trials were included regardless of participant's age, disease status, BP before treatment, or use of other drugs.

Recorded the numbers of participants having one or more CHD events (fatal or non-fatal myocardial infarction [**MI**], or sudden cardiac death), and strokes (hemorrhagic and ischemic could not be distinguished), and the number of participants with a new diagnosis of HF, or exacerbation of existing HF based on new hospital admission or death from HF.

Determined change in BP in the trials (value on entry minus the average value during the trial in the treated group, minus the same change in the control group)

Outcomes were recorded on intention-to-treat basis.

The trials were divided into 3 predefined categories according to whether the recruitment was based on participants having no history of CHD; a history of CHD (acute MI, coronary artery disease with or without recent infarction, or HF); or a history of stroke. .

In trials of participants with no history of vascular disease, BP was usually high, variably defined, and a treat to target approach was used, typically based on one drug with the dose increased before the addition of other drugs to reach the target.^a Control groups were allocated to usual care.

(a I believe that a safer approach would be adding a second drug and a third at lower dose. Adverse effects are more likely to occur at higher doses of a single drug than to idiosyncrasy from several drugs at low dose.)

In trials of participants with a history of CHD, there was generally no selection by BP and no BP target. Treated patients were allocated a specific drug in fixed dose.

In trials of participants with a history of stroke, most followed the treat to target approach.

Also categorized the trials into:

A. Blood pressure difference trials

Designed to achieve a difference in BP between randomized groups who were given, or not given, the study drugs to show effect of this difference on the incidence of CHD events and stroke. Ninety two of the 108 trials were placebo controlled. Some trials used a single drug; some 2 or more drugs.

Summary relative risk estimates from BP difference trials were standardized to a BP reduction of 10 systolic or 5 diastolic.

B. Drug comparison trials:

Compared two BP-lowering drugs with each other. There was no intention to achieve a different BP reduction in one group compared with the other. These trials therefore tested the effects of a drug that were unrelated to lowering BP.

Effect of BP-lowering drugs in lowering BP according to dose:

These estimates were taken from a meta-analysis of 354 short term randomized, placebo controlled trials² of BP-lowering drugs in fixed dose, which showed that the 5 main classes of drugs produced similar reductions in BP when taken at a standard dose, or at the same multiple of standard dose.

It also showed that the BP-lowering effect of the drugs varied with dose and with pre-treatment BP. From the average BP of 154/97, one drug at standard dose lowered BP by 9.1 / 5.5 on average. At lower or higher pretreatment BP, the reduction decreased (or increased) by 0.10 mm Hg systolic and 0.11 mm Hg diastolic in pretreatment BP. The reduction in BP at a pretreatment BP of 150 systolic would be 8.7; at a pretreatment diastolic of 90 would be 4.8.^b

(b These are means. Your patient will differ.)

The estimated BP reduction for two or three drugs at standard dose was calculated by applying the estimated reductions in turn, allowing for the reduction of the first drug in lowering pretreatment BP for the second, and the second for the third. In the example, the pretreatment BP for the second drug would be 141.3/85.3. (150 -8.7 systolic and 90 – 4.7 diastolic).

Using drugs at half standard dose, it was estimated that one, two, and three drugs at half standard dose reduced the pretreatment systolic BP of 150 by 7 , 13, and 20 mm Hg respectively. And pretreatment diastolic of 90 by 4, 7, and 11 mm Hg respectively. (allowing for the effect of one drug in lowering pretreatment BP for the next).^c

(c These are estimates only. Certainly, the reduction will differ in different patients.)

Expected reduction in disease events for a specified reduction in BP:

The association between systolic and diastolic BP and CHD events and stroke were taken from the largest published meta-analysis² This showed that in every age group, CVD mortality plotted on a logarithmic scale against BP on an arithmetic scale is well fitted by straight lines. This indicates a constant proportional change in risk for a specified change in BP from any level of pretreatment BP.^d

(d The proportional reduction is of importance in public health and population studies. Individual patients are not interested in population effects. They are interested in what is going to happen to me. To determine this, absolute differences are required.)

Age specific slopes of the lines permit the calculation of predicted proportional reduction in disease events for any age and BP difference. For example, at age 60-69, the relative risk of stroke is 0.43 for a 20 mm Hg decrease in systolic. For a decrease of 40, the relative risk of 0.43 applies twice.^c This means a relative risk of stroke is 0.18 for a reduction of 40 mm Hg.

Use of 3 drugs at half standard dose in people age 60-69 with a pretreatment BP of 180 systolic is estimated to decrease systolic by 26.9 mm Hg, and to decrease risk of stroke by 68% (RR = 0.32)

(c I do not believe this point has been established.)

RESULTS OF THE META-ANALYSIS OF 147 TRIAL REPORTS INCLUDED IN THE ANALYSIS (108 BP difference trials; 46 drug comparison trials. Seven trials included both.)

To answer the 5 questions above:

1. Do beta-blockers have a special effect over and above lowering BP in preventing coronary heart disease (**CHD**) events in people with a history of CHD?

A. Blood pressure difference trials:

In 37 BP-difference trials of beta-blockers in people with a history of CHD, 32 compared beta-blockers with placebo. CHD events were, on average, reduced by 29%--significantly greater than the 15% reduction in single drug trials of beta-blockers in people without CHD. 27 of the trials recruited participants within a month after a MI. The risk reduction in these trials was 31%. Beta-blockers used within 1 to 2 years after an acute MI were therefore about twice as effective as other drugs in reducing incidence of recurrent MI.^d

(d This is an important clinical point. Beta-blockers should be prescribed immediately post-MI I would start low and go slow. Beta blockers are powerful drugs.)

In 11 trials, beta-blockers were started several years after an MI. In these patients, the risk of recurrence was 13%, similar to the 15% reduction in the other categories of single drug trials.

B. Drug comparison trials:

Four drug-comparison trials of beta-blockers compared with other drugs confirmed the absence of a special effect of beta-blockers in the absence of a recent infarct.

2. Does the effect of BP-lowering drugs in preventing CHD and stroke differ in people with and without a history of cardiovascular disease?

The relative risk estimates of CHD events and stroke in BP difference trials were similar in the three categories of trials (no vascular disease, history of CHD, and history of stroke). There was no difference in effect in people with or without vascular disease.^e

There was no special effect of drugs other than beta-blockers after acute MI.

(e Relative risk reductions may be misleading. Patients with a history of CHD, TIA and stroke are at much higher absolute risk than patients without such a history at any age and at any BP. They should be treated more aggressively.)

3. Does BP reduction alone explain the effect of BP-lowering drugs in preventing CHD and stroke?

A. BP difference trials;

Number of trials ranged from 13 to 37; number of events from 567 to 5019

Relative risk estimates of CHD and stroke for a BP reduction of 10 systolic or 5 diastolic in age group 60-69, the average age at the time of a cardiovascular event:

	CHD events	Stroke
No history of vascular disease	0.79	0.54
History of CHD	0.76	0.65
History of stroke	0.79	0.66
All trials	0.78	0.59

The full potential effect of BP-reductions is achieved within a year.

Relative risk is the same regardless of the history.^e

(e Again, Relative risk reductions may be misleading. Patients with a history of CHD, TIA and stroke are at much higher absolute risk than patients without at any age and at any BP. They should be treated more aggressively.)

B. Single drug trials

Number of trials varied from 22 to 54. Number of events varied from 378 to 4083

Relative risk vs placebo:	CHD events	Stroke
Thiazides	0.86	0.62
Beta-blockers	0.89	0.83
ACE inhibitors	0.83	0.78
Angiotensin receptor blockers	0.86	---
Calcium channel blockers	0.85	0.66

The 5 classes of drug produced relative risk reductions in CHD events that were similar in

magnitude.^f

The reduction in incidence of stroke was smaller in trials of beta-blockers (17%) than in the other 3 classes of drug.

(^f This enables primary care clinicians to offer patients their choice depending on individual tolerance and cost.)

C. Drug comparison trials

CHD events:

When each of the 5 main classes of drug was compared with other classes, the summary relative risk estimates for CHD events were close to 1.0. This indicates no advantage of any one drug over another in the prevention of CHD.

The different classes of drug reduced BP to about the same extent, and reduced CHD to about the same extent, providing evidence of a lack of preventive effects attributable to mechanisms other than lowering BP.

Although the overall risk reductions in CHD events with thiazides was similar to that of other classes of drug, there was an increased risk of sudden cardiac death from using thiazides at very high dose (4 times or higher than standard). Few of the trials used very high doses. Higher doses of thiazides probably cause sudden death.

Stroke:

The summary relative risk estimates for stroke in the drug comparison trials were close to zero with 2 exceptions: There is a suggestion of a greater protective effect of calcium blockers (a reduction in stroke of 33% rather than the 27%.

Beta-blockers had a lesser effect in preventing stroke. (A 19% reduction vs 27%.)

The observed lesser effect of beta-blockers, however, rested on trials of calcium channel blockers vs beta-blockers. Exclusion of these trials weakened the evidence favoring a disadvantage of beta-blockers over the three other classes of drug. But had little effect on the strength of the evidence favoring an advantage of CCBs over the other 3 classes of drug.

The drug comparison trial results were similar and not significantly different when subdivided into three prespecified groups: no vascular disease history; history of CHD; and history of stroke.

4. Should the use of BP-lowering drugs be limited to people with “high” BP ?

A. BP difference trials:

The relative risk estimates of CHD events and stroke in BP difference trials were similar across all levels of BP before treatment, down to 110/70, below which there was little data.

At each BP level, the relative risk reductions were significant and consistent with summary relative risk estimates for all trials: 0.84 for CHD and 0.70 for stroke.

There was no trend in proportional CHD reduction with lower BP before treatment, indicating a constant proportional disease reduction. Ie, the relative risk reduction is constant over all measured levels of BP—the same in people with low as well as high BP.

For stroke, there was a greater risk reduction in trials with the highest systolic and diastolic BP (> 95) due to more intensive treatment in these trials.

Relative risk estimates in BP difference trials according to pretreatment systolic BP:^g

Pretreatment systolic	Relative risk CVD events	Relative risk of stroke
> 170	0.86	0.58
160-169	0.79	0.66
150-159	0.86	0.69
140-149	0.85	0.77
130-139	0.89	0.75
120-129	0.77	0.75
110-119	0.78	0.56

Relative risk estimates were similar for diastolic BP.

(g Again, relative risk reductions are not meaningful to the individual patient who wants to know “What is my risk of an event over the next 10 years”. This will determine the interventions he or she might choose. Compare the relative risk reduction occurring with a reduction in systolic from 165 to 155 ($0.86 \times 0.79 = 0.67$) with a reduction from 135 to 125 ($0.89 \times 0.77 = 0.62$). They are comparable.

But, with the same reduction in BP, the absolute risk reduction is much smaller for those with a lower BP.)

5. What is the quantitative effect of taking one or more BP-lowering drugs in lowering BP and preventing CHD events and stroke ?

	Estimated reduction in systolic BP	Relative risk of CHD age 60-69	Relative risk of stroke. age 60-69
A. One drug at standard dose			
Pretreatment BP			
180	11.7	0.70	0.61

170	10.7	0.72	0.64
160	9.7	0.74	0.66
150	8.7	0.76	0.69
140	7.7	0.79	0.72
130	6.7	0.81	0.81
120	5.7	0.84	0.75
B. Three drugs at half dose			
180	26.9	0.44	0.32
170	24.6	0.47	0.35
160	22.2	0.50	0.39
150	19.9	0.54	0.43
140	17.6	0.55	0.44
130	15.2	0.63	0.53
120	12.9	0.67	0.58

One drug at standard dose reduced the relative incidence of CHD by about 24%, and stroke by 33% in people age 60-69 with a pretreatment systolic BP of 150 and a diastolic of 90.

Three drugs at half standard dose about doubled this effect, reducing relative incidence of CHD by about 45%, and stroke by 60%.^g

(g This is another benefit from prescribing multiple drugs at low dose. Compared with single drug therapy, combinations are more effective as well as safer.)

The data are entirely consistent in showing an age-modifying effect on prevention of CHD events and stroke in relation to reductions in BP.

The proportional effect of age was relatively small. In people 10 years older, the effect of one drug at standard dose was 3% lower on average, and of 3 drugs at half dose was 5% lower. But because mortality from CHD and stroke approximately doubles with each 10 year increase in age, the absolute gain from BP reduction was greater at older age.

If a calcium channel blocker was included in the treatment, its greater benefit in preventing stroke was real, and causal, reducing risk by another 8%.

HEART FAILURE

Beta-blockers without cardioselective and alpha-blocking (vasodilatory) effects [propranolol, oxprenolol, pindolol, and sotalol] lack a preventive effect on HF. Those with these properties have a preventive effect (RR = 0.77)^h

(h Select beta-blockers are very effective drug therapy for patients with HF. Again, start low and go slow.)

In the BP difference trials, CCBs reduced HF by 19%. The drug comparison trials showed CCBs were less effective than the other 4 drugs (RR = 1.22)

Each of the other 4 drugs reduced incidence of HF by 24% on average, with no significant difference in effect between them.

NON-VASCULAR MORTALITY AND ALL-CAUSE MORTALITY:

In the BP-difference trials, there was no increase in cancer mortality or in non-vascular mortality. There were significant relative reductions in all-cause mortality (RR = 0.87), in trials of people with no vascular disease, and in trials of people with a history of CHD, and a history of stroke.

DISCUSSION

1. “This, the largest meta-analysis of randomised trials of blood pressure reduction to date, shows that lowering systolic blood pressure by 10 mm Hg, and diastolic blood pressure by 5 mm Hg using any of the main classes of blood pressure lowering drugs, reduces CHD events (fatal and non-fatal) by about a quarter, and stroke by about a third, regardless of the presence or absence of vascular disease and of blood pressure before treatment, with no increase in non-vascular mortality. Heart failure was also reduced by about a quarter.”
2. Beta-blockers have a special protective effect on people with a clinical history of CHD over and above their BP-lowering effect. This special effect is limited to a few years after an acute MI.
3. With the exception of the short-term effect of beta-blockers, the preventive effect of all 5 classes of BP-lowering drugs is the same or similar in people with and without a history of CVD. There is no reason not to use the drugs for primary prevention as well as secondary prevention.
4. The preventive effect of BP reduction is rapid. The full potential effect is achieved within a year.
5. Quantitative linking of BP reduction and disease prevention:

With the exception of the added benefit of beta-blockers after acute MI, and the possible minor effect of CCBs in reducing risk of stroke, BP reduction explains the action of drugs in preventing CHD and stroke. BP lowering drugs in general do not have material pleotropic effects.

The assessment of beta-blockers as inferior drugs for lowering BP was based on fewer trials than were considered here. They had a similar protective effect on CHD as other drugs, and a greater effect after MI.

The observation that there were no material differences in BP between groups, and no material difference in the relative incidence of CHD or stroke, permits the conclusion that the preventive effects of each class of drug are mediated through BP reduction alone.

6. Proportional disease reduction for a given BP reduction independent of pretreatment BP:

“Our results indicate that the use of blood pressure lowering drugs should not be limited to people with high blood pressure. The proportional reduction in disease events was the same irrespective of blood pressure before treatment down to levels of 70 mm Hg (or lower) for diastolic blood pressure.” “This result, and the previously published trials showing a greater risk reduction for a greater blood pressure reduction whatever the blood pressure, supports a “lower the better” approach to BP reduction.”ⁱ “It means there is medical benefit in lowering a person’s blood pressure whatever the blood pressure, with the logically inescapable conclusion that there is then little or no gain in routinely measuring a person’s blood pressure—a conclusion that will undoubtedly stimulate discussion since it is at variance with 100 years of medical practice.”^j

(i, j Primary care clinicians judge the benefit / harm-cost ratio of interventions one-patient-at-a-time. Older patients with higher BP do indeed have greater absolute risk of CHD and stroke. The benefit / harm-cost ratio of reducing BP will be higher in a patient age 65 with a systolic of 140 than in a 40 year old. And in a patient with a history of CHD or stroke than in one without.

At a certain point (eg, at a lower BP) harms (even if rare) and costs of drug therapy will outweigh benefits. The benefit / harm-cost ratio will be reversed. This is a matter of individual judgment.

I believe long-term compliance with a drug regimen will be very poor in patients who do not have regular follow-up and encouragement.

The authors focus on the benefits of drug therapy in reducing BP. Other risk factors obviously must be considered –lipids, obesity, fitness, and the benefit of long-term low dose aspirin in patients with a history of CHD or stroke. Attention to these factors will modify the benefits of BP reduction alone.

7. Comorbidities:

The claimed advantages of one drug over another for an individual who has an existing disease are generally of minor importance. All classes of drugs are effective in heart failure (non-cardioselective beta blockers apart) and after MI (the greater effect of beta blockers apart).

CCBs seem to be less effective than other drugs in heart failure but the differences in risk reduction are not large.

All classes of drugs prevent headache and migraine.

There is no evidence to support recommendations for particular classes of drug in older and younger people.

Thiazides prevent renal calculi and may prevent hip fracture.

Beta blockers are advantageous in glaucoma.

ACE and ATRB reduce the incidence of diabetes, and diabetic and non-diabetic nephropathy.

Using the drugs in combination rather than singly therefore offers several medical benefits.

8. Adverse effects

Patients should be monitored for side effects of drugs and a drug should be withdrawn if adverse effects occur.^k

(**k** *The authors admit that adverse effects may occur.*)

The prevalence of adverse effects is strongly related to dose. Low dose combination therapy can greatly improve safety.

ACE inhibitors or ATRB in combination with thiazides counter the potential hazard of hypokalemia.

The diabetogenic effect and the increase in uric acid from thiazides is low when given at half dose.

ACE and angiotensin receptor blockers are teratogenic and should be avoided in pregnancy.

Thiazides are related to sexual dysfunction. Not so with the other drugs.

It is difficult to defend the widespread practice of tailoring treatment. The case for individualizing BP lowering therapy disappears with low dose combination therapy based on three drugs.

9. Cost

Is another reason for selecting drugs. All but ATRBs are generic and ATRBs will become so soon.

10. Absolute risk reduction:

The preventive potential must be assessed in terms of absolute risk reduction, which may be converted by multiplying relative risk reduction by the incidence in a specified population. At age 65, the 10-year risk of MI in England is estimated to be about 10% in men and 5% in women. Given the average BP at that age of 150/90, the expected relative risk reduction using three drugs at half dose is 46%. The absolute reduction over 10 years in men is then 4.6% and 2.3% in women. The corresponding absolute risk reduction for stroke is 2.9% for men and 2.3% for women. For MI + stroke is 7.5% for men and 4.6% for women.^L

(**L** *Again, at a younger age, and at a lower BP, absolute risk will be much lower. Not all persons will benefit from BP reduction.*)

Demonstrating the value of treatment in everyone in a population above a particular age might be perceived as “medicalizing” a population. “We disagree with this view.” Identifying people with a relatively high BP for their age, giving them the diagnosis “hypertension” clearly medicalizes the

individual. Offering BP lowering treatment to a population above a certain age, regardless of their BP, on the basis that it would prevent a future heart attack and stroke with minimal adverse effects does not medicalize the population, unless the broad view is taken that anyone who takes a preventive agent regularly is medicalized. Such a broad view would mean that people receiving antimalarials, vaccines, or contraceptive drugs are medicalized.

The preventive effect of lowering BP is substantial and capable of reducing incidence of CHD and stroke by at least half in all people at risk of CHD events or stroke, whatever the BP and whatever the basis of being at risk—having a history of cardiovascular disease event or simply being older.

“Our results support the view that blood pressure lowering drugs should no longer be regarded as treatment for hypertension. Consideration should be given to replacing current policies that focus on routinely measuring blood pressure with policies that focus on routinely lowering blood pressure.”^k

(K Routinely lowering BP in everyone is too broad an application.)

BMJ May 23, 2009; 1245-53 Original investigation by M R Law, J K Morris, and N J Wald, Barts and The London School of Medicine, Queen Mary University, London, UK

1 Age-specific relevance of usual blood pressure at vascular mortality: A meta-analysis of individual data from one million adults in 61 prospective studies. Lancet 2002; 360: 1902-13

2 Value of low dose combination treatment with blood pressure lowering drugs: analysis of 354 randomised trials. BMJ 2003; 326: 1427-31

Wald and Law are the originators of the “polypill”, a combination of 3 antihypertension drugs, a statin, and aspirin, all at low dose. They suggested the pill be taken by all persons over age 55 without pre-testing or post-testing. They estimated this would lower incidence of CHD by 80%.

I wrote this abstract from the extended article I downloaded from BMJ.com. The print article in the May 23 2009 BMJ is abridged.

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5-2 EFFECT OF CLOPIDOGREL ADDED TO ASPIRIN IN PATIENTS WITH ATRIAL FIBRILLATION

In patients with atrial fibrillation (AF), adjusted-dose vitamin K antagonists (warfarin in the USA) and antiplatelet agents reduce the risk of stroke by 64% and 22% respectively. Warfarin is related to almost double the risk of hemorrhage (including intracranial hemorrhage) compared with aspirin.

Warfarin is usually recommended for patients at higher risk for stroke, and aspirin for patients at lower risk. Warfarin requires regular monitoring. It interacts with other drugs, and some foods.

In patients with acute coronary syndromes clopidogrel combined with aspirin has added benefits over aspirin alone.

This study assessed whether clopidogrel + aspirin would reduce risk of thromboembolic stroke and other major vascular events in patients with AF to a greater degree than aspirin alone. And whether clopidogrel + aspirin would lead to greater risk of hemorrhage.

STUDY

1. This double-blind, randomized trial in 580 centers in 53 countries followed over 7500 patients with AF (mean age 71). All subjects had AF at entry or had at least two episodes of AF in the past 6 months. They were considered “unsuitable” for warfarin therapy.
2. All had at least one risk factor for stroke: age over 75, hypertension, previous stroke or TIA, or other systemic embolization, a left ventricular ejection fraction under 45%, peripheral vascular disease, diabetes, or coronary artery disease.
3. None had risk factors for hemorrhage: peptic ulcer disease, thrombocytopenia, history of intracerebral hemorrhage, or alcohol abuse.
4. Randomized to: 1) aspirin (75-100 mg daily) + placebo (**aspirin-alone**), or 2) clopidogrel (*Plavix*; Bristol Myers Squib; 75 mg daily) + aspirin . (**C + A**)
5. Primary outcome = combination of stroke, myocardial infarction, non-CNS systemic embolization, or death from vascular causes.
6. Follow-up for a median of 3.6 years.

RESULTS

1. Outcomes (% per year)	C + A	Aspirin-alone	Absolute difference	NNT*
Primary outcome	6.8	7.6	0.8	125
Any stroke	2.4	3.3	0.9	111
Ischemic stroke	1.9	2.8	0.9	111
Hemorrhagic stroke	0.2	0.2	--	
Non-disabling stroke	0.9	1.2	0.3	333
Disabling or fatal stroke	1.6	2.1	0.5	200

(All differences were statistically significant. Difference was primarily due to a reduction in stroke

with C + A. *NNT = number needed to treat for one year with C + A vs aspirin-alone to benefit one patient)

2. Myocardial infarction, non-CNS systemic embolization, death from cardiovascular causes, and death from any cause did not differ between groups.

3. Risks of hemorrhage (%/y):	C + A	Aspirin alone	Absolute difference	NNH*
Major bleeding	2.0	1.3	0.7	143
Minor bleeding	3.5	1.4	2.1	47
Intracranial bleeding	0.4	0.2	0.2	500

(Bleeding was more frequent in the C + A group; *NNH = number needed to treat for one year with C + A vs aspirin-alone to harm one patient.)

4. At 4 years, rates of discontinuation was about 38% in both groups.¹ Many on discontinuation began warfarin therapy.

5. Subgroup analysis: (%/ year)

	Primary outcome		Stroke	
	C + A	A-alone	C + A	A-alone
Age > 75	10.56	10.41	3.37	3.61
Paroxysmal AF	4.97	5.07	1.76	2.23
CHADs score ²				
>1	9.02	9.58	2.98	4.00
1	4.97	5.07	1.68	2.40

(Little or no benefit from C + A in these subgroups.)

DISCUSSION

1. The addition of clopidogrel to aspirin (as compared with aspirin alone) reduced the rate of major vascular events from 7.6% per year to 6.8% per year, primarily due to a reduction in stroke.

(NNT for one year to prevent one major vascular event = 125; to prevent one stroke = 111.)

2. The rate of major hemorrhage increased with the addition of clopidogrel to aspirin from 1.3% to 2.0% (NNH = 143)

3. Therapy with warfarin is more effective than C + A in preventing thrombo-embolic stroke, but is associated with greater risk of hemorrhage. “It is important to emphasize that oral anticoagulation with a vitamin K antagonist is the preferred and recommended therapy for the prevention of ischemic stroke in patients with atrial fibrillation.”

4. Use of C + A did not result in a significant reduction in mortality from any cause. The majority

of deaths in this study were due to arrhythmia, heart failure, and non-vascular causes.

CONCLUSION

In patients with AF for whom warfarin therapy was unsuitable, the addition of clopidogrel to aspirin reduced the risk of major vascular events, especially stroke, and increased the risk of major hemorrhage.

NEJM May 14, 2009; 360: 2066-78 Original investigation by the ACTIVE Investigators, principal investigator S J Connolly, McMaster University, Hamilton, Ontario, Canada

1 This certainly reduces effectiveness of C + A.

2 CHADS score: Congestive heart failure 1 point; Hypertension 1 point; Age > 75 1 point; Diabetes 1 point; previous Stroke or TIA 2 points. Patients with a score of 0 or 1 are usually considered at low risk for stroke. Many authorities recommend aspirin-alone for this group.

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Should Be Used for Secondary Prevention. Use for Primary Prevention Is Debatable.

5-3 ASPIRIN IN THE PRIMARY AND SECONDARY PREVENTION OF VASCULAR DISEASE

A Collaborative Meta-Analysis Of Individual Participant Data From Randomised Trials

Long-term, low-dose, aspirin is of definite and substantial benefit for many people who already have occlusive vascular disease and are at high risk for recurrence. (Secondary prevention) Long-term aspirin therapy in these persons reduces the yearly risk of serious vascular events (non-fatal MI, non-fatal stroke, and vascular death) by about a quarter. This decrease typically corresponds to an absolute reduction of about 10-20 per 1000 in yearly incidence of non-fatal events and to a smaller, but still defiant, reduction in vascular death.

Against this benefit, the absolute increase in major gastrointestinal bleeding is an order of magnitude smaller.

Thus, for secondary prevention, benefit of long-term low-dose aspirin substantially exceeds the risk of bleeding.

For primary prevention, the balance is less clear. The absolute benefits in primary prevention are generally on order of magnitude lower than in secondary prevention.

Current guidelines largely ignore any differences in bleeding risk and recommend that aspirin be used widely for primary prevention in those at moderately raised risk for coronary heart disease (**CHD**).

It has also been suggested that, since age is a major determinate of risk of CHD, aspirin should be started in all people above a specific age.

The alternative to primary prevention is deferral of the start of aspirin until some evidence of occlusive vascular disease is noted. The disadvantage of this approach is that the first manifestation of disease might be a disabling or fatal event; the advantage is that it could avoid decades of slightly increased risk of cerebral hemorrhage or major extracranial bleeding.

This collaborative meta-analysis of individual participant data involved large trials of primary prevention with aspirin.

A meta-analysis of previous secondary prevention trials of aspirin compared the absolute effects of aspirin in secondary vs primary prevention trials

STUDY

1. Primary prevention trials were eligible only if they involved a randomized comparison of aspirin vs no aspirin. Persons with any history of occlusive vascular disease and diabetes were excluded. Six primary prevention trials (95 000 persons) were included.
2. Secondary prevention trials included individuals with previous myocardial infarction, stroke, or transient ischemic attack (16 trials; 17 000 persons) that compared long-term aspirin vs controls.
3. Comparisons were intention-to-treat analyses of first events of treated participants vs controls.
4. Main outcomes were serious vascular events and major extracranial bleeding, usually defined as a bleed requiring transfusion or resulting in death.

RESULTS

1. Aspirin dose varied from 75 mg to 500 mg per day in the primary prevention trials.
2. Yearly absolute difference (% per year aspirin vs control):

	Primary prevention	Secondary prevention
Major coronary event	-0.06 %	-1.00 %
Non-fatal MI	-0.05	-0.66
CHD mortality	-0.01	-0.34
Stroke	-0.01	-0.46
Vascular death	-0.01	-0.29
Any serious vascular event	-0.07	-0.29
Major extracranial bleed	+0.07	a

(a. Extracranial bleeding incompletely reported.)

3. Primary prevention trials: The NNT (number needed to treat to benefit one patient over one year) varied from 1111 to 10 000. The number needed to treat to harm (NNTharm) one primary prevention patient per year (major hemorrhage) = 1428.
4. Secondary prevention trials: The NNT to benefit one patient per year varied from 100 to 344—about ten times the benefit in primary prevention. (*I assume the bleeding complications (NNTharm) were comparable to those in primary prevention trials. RTJ*)

DISCUSSION

1. The availability of individual participation data for the present meta-analysis has allowed a more reliable comparison of the benefits and hazards of aspirin in apparently healthy people (primary prevention).
2. The absolute benefits of aspirin are an order of magnitude smaller in primary than in secondary prevention trials.
3. In the primary prevention trials, the proportional reduction in serious vascular events did not depend on age or sex.
4. In the secondary prevention setting, aspirin would be of substantial net benefit (irrespective of age and sex). It would reduce non-fatal vascular events by much more than it would increase major extracranial bleeds and, despite adverse effects of cerebral hemorrhage, it would reduce overall vascular mortality.
5. Many patients with a history of vascular disease would have their risks of recurrence reduced substantially by statins, other modern drugs, and by appropriate vascular procedures. If risks are approximately halved by these interventions, the absolute benefit of aspirin in secondary prevention would be reduced by half.
6. In the primary prevention trials, the absolute risk of a serious vascular event among people of a given age and sex was an order of magnitude less than in secondary prevention trials.
7. In primary prevention, the absolute reduction in occlusive events would be only about twice as large as the absolute reduction in bleeding. Moreover, these trials of aspirin were mainly in people who were not taking statin therapy, which would have reduced both myocardial infarction and ischemic stroke with little hazard.
8. Primary prevention with a statin could well be preferred to primary prevention by aspirin only. If so, then one of the main questions for aspirin in primary prevention nowadays is whether to add it to a statin. If the risk of occlusive vascular disease is already approximately halved by statins, then further absolute benefit of adding aspirin could be only about half as large as was suggested by

primary prevention trials. In that case, the benefits and hazards of adding long-term aspirin in people without preexisting disease might be of approximately similar magnitude.

9. There is still a possibility that there is some particular category of individuals in whom primary prevention with aspirin is of definite benefit. Adults with diabetes may benefit more.
10. Only 9% of participants in the six primary prevention trials had a predicted CHD incidence above 1% per year, so the present results among them are not reliable.
11. Present primary prevention guidelines recommend that aspirin be given to those at risk of CHD exceeding a particular threshold. These guidelines assume that the absolute risk of bleeding remains the same irrespective of the absolute risk of CHD, or that risk of bleeding depends solely on age. The present analysis suggests there are risk factors for bleeding in addition to age, including male sex, diabetes, current smoking, elevated BP, cholesterol levels, and body mass index.
12. Even in people at moderately increased risk of CHD, the absolute benefits and harms of adding aspirin to a statin-based primary prevention regimen could still be approximately evenly balanced.
13. In primary prevention, the net absolute reduction in disabling and fatal occlusive events is likely to be small, and at least partially offset by a small increase in serious bleeding.
14. Drug safety is of particular importance in public health recommendations for large apparently disease-free populations. There should be good evidence that benefits exceed risks by an appropriate margin.
15. Currently available trial results could well inform personally appropriate judgments by individuals about their own use of long-term aspirin.

CONCLUSION

For primary prevention in persons without previous vascular disease, aspirin is of uncertain net value. Reductions in occlusive events should be weighed against the increased risk of major bleeding.

For secondary prevention, benefits of long-term aspirin outweigh risks.

Lancet May 30, 2009; 373: 1849-60 Original investigation by the Antithrombotic Trialists' Collaboration, Richard Doll Building, Oxford, UK

An editorial in this issue of Lancet (p 1822-23), first author Ale Algra, University Medical Centre Utrecht, Utrecht, Netherlands comments and expands on this article:

How can we use this study in daily practice?

The ATC investigators try to balance benefits and risks of long-term aspirin without taking into account the consequences of both harms and benefits on quality of life.

The editorialists updated their previous cost-analysis with the new data provided by the ATC investigation. They concluded that benefits of long-term aspirin outweigh harms in some subsets of patients:

For men:

Age 60-69 at twice the 10-year average risk and above for a vascular event.

Age 70-79 at average risk and above.

For women:

Age 60-69 at five times average risk and above

Age 70-79 at twice average risk and above.

The editorialists state that risks and benefits do differ between men and women. (Contrary to the findings of the meta-analysis.)

Quality of life should be considered on an individual basis. Would you rather experience a myocardial infarction or a gastrointestinal hemorrhage?

Some patients may wish not to be medicalized. Individual preference matters.

The Current Evidence Is Insufficient To Rule Out A Small Yet Important Benefit

5-4 ASPIRIN FOR THE PREVENTION OF CARDIOVASCULAR EVENTS IN PATIENTS WITH PERIPHERAL VASCULAR DISEASE: A Meta-analysis of Randomized Trials

The effect of long-term, low dose aspirin on patients with peripheral artery disease (**PAD**) is uncertain. In a group of over 9200 patients with PAD, the Antithrombotic Trialists' Collaboration, antiplatelet therapy vs placebo was associated with a statistically significant 23% reduction in cardiovascular events. However, nearly 2/3 of the participants took antiplatelet agents other than aspirin.

The uncertain benefit of aspirin in PAD was further raised by a recent large randomized controlled trial involving patients with diabetes and PAD, which showed no benefit in reducing cardiovascular events.

Despite the paucity of data, major guidelines support the use of aspirin as first-line therapy for patients with PAD. However, the FDA concluded that there is insufficient evidence to support a labeling indication for aspirin in patients with PAD.

This meta-analysis evaluated all the available evidence from prospective, randomized trials of aspirin alone, or in combination with other antiplatelet drugs, in prevention of cardiovascular events in

patients with PAD. It tested the null hypothesis that aspirin was not different from placebo in reducing risk of the combined primary endpoint of non-fatal MI, non-fatal stroke, and cardiovascular death.

STUDY

1. A literature search found 18 prospective, randomized trials of aspirin, with or without dipyridamole (5269 individuals with PAD). Aspirin dose ranged from 100 mg/d to 1500 mg/d for monotherapy, and from 25 mg aspirin + 75 mg dipyridamole to 325 mg aspirin + 75 mg dipyridamole.
2. Inclusion criteria: 1) prospective, randomized trials, 2) assignment of PAD patients to aspirin vs a placebo or control group, 3) data available on all-cause mortality, cardiovascular death, MI, and stroke.
3. Patients with PAD included those with claudication, those undergoing percutaneous intervention or bypass surgery, and asymptomatic patients with a reduced ankle/brachial BP ratio. Most of the trials predated 1995 and included many patients with advanced peripheral atherosclerosis.
4. Primary endpoint = cardiovascular events (non-fatal MI, non-fatal stroke, and cardiovascular death).
5. Follow-up ranged from 10 days to 7 years.

RESULTS

1. A total of 251 cardiovascular events (the primary endpoint) took place among 2823 patients receiving any aspirin vs 169 among 2446 controls (8.9% vs 11%; 12% reduction). The difference was not statistically significant.
2. The risk of non-fatal stroke was lower in the aspirin group (1.8% vs 3.1%). This was statistically significant.
3. Bleeding was not significantly increased (1.8% vs 1.8%). However, bleeding was not formally adjudicated or reported in most studies, which limits the ability to establish the association.
4. Effect of aspirin monotherapy on the primary outcome: 125 cardiovascular events among 1516 patients vs 144 events among 1516 controls (8.2% vs 9.6%; not significant). Aspirin monotherapy was associated with a significant reduction in non-fatal stroke (2.1% vs 3.4%).
5. Two trials compared aspirin monotherapy with placebo using low dose (100 mg): 112 cardiovascular events occurred among 823 participants vs 127 events among 819 placebo participants (13.6% vs 15.5%). Although not statistically significant, the population studied was small, and the 95% confidence interval was wide, potentially limiting detection of important cardioprotective events.

DISCUSSION

1. “Results of this meta-analysis demonstrated that, for patients with PAD, aspirin therapy alone or in combination with dipyridamole did not significantly decrease the primary endpoint of cardiovascular events.” This may reflect limited statistical power. Smaller levels of benefit, such as a 20% reduction, cannot be excluded with the available evidence.
2. Aspirin was associated with a significant reduction of non-fatal stroke.
3. There was no significant benefit noted for non-fatal MI, cardiovascular mortality or all-cause mortality.
4. These findings in patients with PAD contrast with the literature that supports a more definitive role of aspirin in the treatment of symptomatic coronary heart disease and cerebrovascular disease.
5. Patients with PAD have been underrepresented in randomized trials.
6. Patients with PAD are at heightened risk for CVD events because of increased atherothrombosis burden, endothelial dysfunction, platelet activation, insulin resistance, and diabetes. They may represent a diffuse form of atherosclerosis with a high inflammatory burden and platelet activation. They may be less responsive to aspirin.
7. Because aspirin reduces cardiovascular morbidity and mortality in other high risk populations, and because it is inexpensive, many physicians and guidelines recommend aspirin as first line therapy for PAD.
10. In most trials in this meta-analysis, major bleeding events were not formally assessed. Therefore a risk/benefit analysis was not performed.
11. There is a critical need for future comparative studies of aspirin and newer, more potent antiplatelet agents designed to assess the long-term risks and benefits in PAD patients.

CONCLUSION

This meta-analysis did not demonstrate a significant benefit of aspirin vs placebo on cardiovascular events in patients with PAD. Aspirin significantly reduced risk of non-fatal stroke.

The current evidence is insufficient to rule out a small yet important benefit.

JAMA May 13, 2009; 301: 1909-19 Meta-analysis, first author Jeffrey S Berger, University of Pennsylvania, Philadelphia, PA

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