Coronary heart disease prevention: insights from modelling incremental cost effectiveness

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Editorial by Warburton

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Abstract

Objective To determine which treatments for preventing coronary heart disease should be offered to which patients by assessing their incremental cost effectiveness.
Design Modelling study
Data sources Cost estimates (for NHS) and estimates of effectiveness obtained for aspirin, antihypertensive drugs, statins and clopidogrel.
Data synthesis Treatment effects were assumed to be independent, and cost per coronary event prevented was calculated for treatments individually and in combination across patients at a range of coronary risks.
Results The most cost effective preventive treatments are aspirin, initial antihypertensive treatment (bendrofluazide and atenolol), and intensive antihypertensive treatment (bendrofluazide, atenolol and enalapril), whereas simvastatin and clopidogrel are the least cost effective (cost per coronary event prevented in a patient at 10% coronary risk over five years is £3500 for aspirin, £12 500 for initial antihypertensives, £18 300 for intensive antihypertensives, £60 000 for clopidogrel, and £61 400 for simvastatin). Aspirin in a patient at 5% five year coronary risk costs less than a fifth as much per event prevented (£7900) as simvastatin in a patient at 30% five year risk (£40 800).
Discussion A cost effective prevention strategy would offer aspirin and initial antihypertensive treatment to all patients at greater than 7.5% five year coronary risk before offering statins or clopidogrel to patients at greater than 15% five year coronary risk. Incremental cost effectiveness analysis of treatments produces robust, practical cost effectiveness rankings that can be used to inform treatment guidelines.

Introduction

Preventing coronary heart disease has assumed increasing importance in UK health policy.[1] Several treatments reduce risk of coronary disease, the absolute benefits being proportional to pretreatment risk, and individual patients may be eligible for more than one treatment. It is argued that treatments for lowering blood pressure and cholesterol are equally effective whether or not blood pressure or cholesterol levels exceed arbitrary thresholds.[2] This means that virtually all patients might benefit from risk lowering treatments.

Given that health service resources are finite, a rational approach to treatment would offer patients treatments in order of their expected cost effectiveness. This requires knowledge of the incremental benefits of risk lowering treatments in relation to their incremental costs. Incremental cost effectiveness analysis provides a means of ranking treatments by calculating the incremental changes in both costs and benefits. This paper presents an incremental cost effectiveness analysis of risk lowering treatments in patients at varying levels of risk. The treatments analysed are aspirin, initial antihypertensive treatment, intensive antihypertensive treatment, a statin, and clopidogrel.

Methods

Costs

Costs are considered from the perspective of the health service and are discounted at 6% per year.[3] There are two main components to the costs of long term treatment—follow up costs and prescribing costs.

Follow up costs are based on the cost of two clinic appointments a year with a practice nurse,[4] and the cost of blood tests. Patients taking thiazide diuretics require annual measurement of serum electrolytes and uric acid. Patients taking statins require annual measurement of serum lipid concentrations and liver function tests.

Prescribing costs include drug[5] and dispensing costs.[6] Initial antihypertensive treatment is with bendrofluazide (bendroflumethiazide) 2.5 mg and atenolol 50 mg; further antihypertensive treatment adds enalapril 20 mg to these treatments. Cholesterol lowering is with simvastatin 40 mg. Clopidogrel is given at a dose of 75 mg daily.

Effectiveness

I calculated benefits of treatment as major coronary events (myocardial infarctions, new cases of angina, and cardiac deaths) prevented over five years, with the benefits discounted at 1.5% per annum in keeping with current guidelines from the National Institute for Clinical Excellence.[3]

In the base case analysis, I calculated cost effectiveness for a patient whose pretreatment five year coronary risk is 10%.[7] This is the coronary risk of a non-diabetic, non-smoking man aged 62 with blood pressure of 160/98 mm Hg, total serum cholesterol concentration of 6.5 mmol/l, and high density lipopro-

Table 1 Average costs, effects, and cost effectiveness of preventive treatments in a patient at 10% risk of a coronary event over five years

			Absolute risk reduction per 5 years		Discounted costs per 5 years*				
Treatment	Relative risk with treatment (A)	Adverse event rate per 5 years (B)	Simple (C=10%×(1–A)–B)	Discounted (D=C×(discount factor))	Prescribing (E)	Laboratory investigations (F)	Follow up (G)	Total (H=E+F+G)	Cost per event prevented (I=H/D)
Aspirin 75 mg	0.72	0.3%	2.5%	2.4%	£19	£0	£65	£85	£3 500
Bendrofluazide 2.5 mg + atenolol 50 mg	0.83	0.0%	1.7%	1.7%	£124	£19	£65	£208	£12 600
Bendrofluazide 2.5 mg, atenolol 50 mg, + enalapril 20 mg*	0.67	0.0%	3.3%	3.2%	£497	£19	£65	£581	£18 300
Clopidogrel 75 mg	0.63	0.0%	3.7%	3.6%	£2071	£0	£65	£2136	£60 100
Simvastatin 40 mg	0.69	0.0%	3.1%	3.0%	£1744	£39	£65	£1848	£61 400

*Costs have been discounted at 6% and benefits at 1.5% in accordance with NICE guidelines.

tein cholesterol concentration of 1.3 mmol/l. Under current guidelines he is eligible for antihypertensive treatment, a statin, and aspirin.[8]

For each intervention, I derived relative risk of coronary heart disease from a recent meta-analysis (see bmj.com for details), and these are shown in column A of table 1. Aspirin also increases the incidence of major bleeding by 0.3% (0.2% to 0.4%) over five years of treatment.[9] To take account of this, I offset the absolute reduction in coronary risk over five years by 0.3%.

If treatment effects are independent the relative risk with two or more treatments is the product of the relative risk on each treatment. For example, the relative risk of a coronary event with aspirin is 0.72, with a statin is 0.69, and with aspirin and a statin is 0.50 (0.50 = 0.72×0.69).

Average cost effectiveness

I calculated the cost of each intervention over a five year time horizon, and calculated the reduction in absolute coronary risk by subtracting post-treatment risk from pretreatment risk. Post-treatment risk is the product of pretreatment risk and the relative risk with treatment. In the case of aspirin, 0.3% is subtracted from the reduction in absolute coronary risk to take account of major adverse effects. The cost effectiveness ratio (cost per event prevented) is the total cost divided by the reduction in absolute coronary risk.

In a sensitivity analysis I calculated maximum and minimum costs per event prevented for each of the interventions using the upper and lower 95% confidence limits for effectiveness. The average cost effectiveness rankings inform the order in which treatments would be offered in an incremental cost effectiveness analysis. To test the robustness of cost effectiveness rankings, I explored the effects of changes in the costs of interventions and the frequency of adverse effects alongside changed assumptions about effectiveness.

Incremental cost effectiveness

An efficient prevention strategy would offer the most cost effective treatment first, then the next most cost effective treatment, and so on. The incremental cost effectiveness ratio is the additional cost associated with adding each treatment divided by the additional benefit of the treatment. The incremental cost per event prevented is calculated in much the same way as the average cost per event prevented (see bmj.com).

A sensitivity analysis tested the robustness of cost effectiveness ratios by changing assumptions about effectiveness and identifying the threshold costs at which cost effectiveness rankings would change. Since the cost per coronary event prevented decreases as patients' coronary risk increases, I also investigated the cost effectiveness of coronary disease prevention in patients at a range of five year coronary risks.

Results

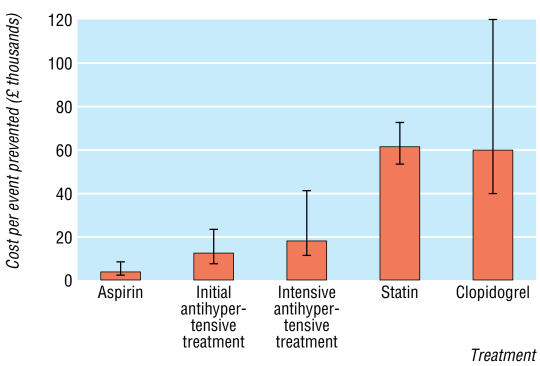
Average cost effectiveness

In a patient at 10% coronary risk over five years, aspirin is the most cost effective risk lowering treatment (see table 1 and figure). The sensitivity analysis showed that, for simvastatin to be of similar cost effectiveness to intensive antihypertensive treatment, the relative risk with treatment must be at the lower 95% confidence interval and the cost of the drug 65% lower. This is unlikely, as drug prices typically fall by less than 50% when they come off patent. There is a wide degree of uncertainty about the cost effectiveness of clopidogrel, reflecting uncertainty about the relative risk on treatment.

Cost effectiveness of initial and intensive antihypertensive treatment is sensitive to increases in the price of drugs. If sufficiently high cost drugs are used (such as for brand name calcium channel blockers) the cost per event prevented with initial antihypertensive drugs is as high as with a statin.

Incremental cost effectiveness of additional treatments

The incremental costs of additional treatments include only additional drug costs and additional laboratory investigations. The incremental effectiveness of additional drugs is also smaller than their effectiveness as



Average cost effectiveness of preventive treatments in a patient at 10% risk of a coronary event over five years. (Error bars represent cost per coronary event prevented if effectiveness is at upper and lower 95% confidence limit)

Table 2 Incremental costs of preventive treatments in combination per event avoided in a patient at 10% risk of a coronary event over five years

Additional treatment	Incremental relative risk with treatment (A)	Adverse event rate per five years (B)	5 year coronary risk with this treatment (C=10%×(cumulative product of A))*	Incremental risk reduction: Simple (D=C×A−B)	Incremental risk reduction: Discounted (E=D×(discount factor))	Incremental cost: Discounted (F)	Incremental cost: Per event prevented (G=F/E)
Aspirin 75 mg + follow up	0.72	0.3%	7.2%	2.5%	2.4%	£85	£3 500
Bendrofluazide 2.5 mg + atenolol 50 mg	0.83	0.0%	6.0%	1.2%	1.2%	£143	£12 000
Enalapril 20 mg	0.81	0.0%	4.8%	1.1%	1.1%	£374	£33 900
Simvastatin 40 mg	0.69	0.0%	3.3%	1.5%	1.5%	£1783	£122 400
Clopidogrel 75 mg (replaces aspirin)†	0.88	0.0%	2.9%	0.4%	0.4%	£2051	£527 200

*10% (risk with no treatment) multiplied by cumulative product of A (A for each of the rows above (the effects of all previous treatments)).
†Because clopidogrel is not prescribed with aspirin, it replaces aspirin in the incremental analysis; this results in clopidogrel having the highest incremental cost per event prevented even though it had only the second highest individual cost per event prevented.

initial treatments, because incremental effects act on progressively smaller pretreatment risks.

If a patient at 10% five year coronary risk is given combination treatments in order of their cost effectiveness, the incremental cost per event prevented rises with each additional treatment. Compared with placebo, clopidogrel is more cost effective than simvastatin. However, clopidogrel as a replacement for aspirin provides little additional benefit at substantial extra cost. It is therefore the least cost effective in an incremental analysis. Table 2 shows the incremental costs per event prevented.

The sensitivity analysis showed that the most favourable assumption for simvastatin is that relative risks for all other treatments are at the upper 95% confidence limit and for simvastatin is at the lower 95% confidence limit. If this is the case, the incremental costs per event prevented are £8700 for aspirin, £18 800 for initial antihypertensive treatment, £243 000 for intensive antihypertensive treatment, £65 800 for simvastatin, and £177 300 for clopidogrel. Even under these assumptions, the price of simvastatin would have to fall by 70%, and the price of clopidogrel by more than 90%, to be of similar cost effectiveness to initial antihypertensive treatment.

Further analysis

Under the base case analysis, the cost effectiveness rankings of all five treatments are the same for any patient with a five year coronary risk greater than 1.5%. The incremental cost per event prevented in a patient at 5% five year coronary risk is £7900 with aspirin and £24 000 with initial antihypertensive treatment. This is less than the incremental cost per event prevented with simvastatin (£40 800) in a patient at 30% five year coronary risk (see bmj.com).

The most extreme assumptions we can make are to assume that relative risk on all treatments is at the upper 95% confidence limit (least effective) and assume that the relative risk with simvastatin is at the lower 95% confidence limit (most effective). Under these assumptions, the cost per event prevented with aspirin in a patient at 7.5% five year risk would be £12 900 and the cost per event prevented with simvastatin in a patient at 15% five year risk would be £13 200.

Discussion

This analysis confirms the poor cost effectiveness of statins and clopidogrel compared with aspirin and antihypertensive treatment,[10 11] and suggests it is likely to be more cost effective to treat patients at 5% five year coronary risk with aspirin than to prescribe further antihypertensive treatment or statins to patients at 30% five year risk.

Limitations of study

Some of the findings are sensitive to the choice of drug. This is particularly true of the cost effectiveness of initial antihypertensive treatment, where drug prices range from £10 to £290 a year. However, consideration of every possible antihypertensive regimen is beyond the scope of this paper.

The analysis may overestimate the benefits of some interventions. Estimates of the effects of intensive antihypertensive treatment are derived from studies comparing less intensive with more intensive treatment.[12] But the estimate of the benefits of initial antihypertensive treatment include all blood pressure lowering, not just less intensive treatment.[13] The additional benefits of intensive antihypertensive treatment may therefore be exaggerated.

Apart from major bleeding due to aspirin, the analysis takes no account of adverse effects of treatment. However, major irreversible adverse event rates would have to be 0% with a statin and to exceed 2.5% per five years with aspirin and 1.3% with initial antihypertensive treatment for the statin to be more cost effective than the latter two treatments. Even if all patients who experience adverse effects discontinue

What is already known on this topic

Aspirin, antihypertensive treatment, statins, and clopidogrel are all effective in preventing coronary heart disease

These drugs vary in their cost effectiveness, and a rational prevention strategy would offer the most cost effective treatments first

What this study adds

Most of the benefits of prevention can be achieved with aspirin and antihypertensive treatment at a fraction of the cost of simvastatin or clopidogrel

Treating a patient with a five year coronary risk of 7.5% with aspirin and low cost antihypertensives is more cost effective than treating a patient with 30% coronary risk with a statin

Clinical guidelines should be informed by analysis of the incremental costs and incremental benefits resulting from each additional treatment

treatment but continue to be followed up, this makes no difference to the cost effectiveness rankings.

Conclusion

Incremental cost effectiveness analysis of treatments produces robust, practical cost effectiveness rankings. Authors of guidelines should take account of this when making treatment recommendations. If the aim of treatment is to maximise prevention of coronary disease, these results cast doubt on present policy, which emphasises achievement of target blood pressures and the use of statins for people at 15% five year risk of a coronary event.[14] A more efficient prevention strategy would be to offer aspirin and initial antihypertensive treatment to all people at over 7.5% five year coronary risk before offering statins to patients at 30% five year risk. According to national survey data, 87% of men and 56% of women aged over 65 are at over 7.5% five year risk.[15]

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Predictive accuracy of the Framingham coronary risk score in British men: prospective cohort study

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Abstract

Objective To establish the predictive accuracy of the Framingham risk score for coronary heart disease in a representative British population.
Design Prospective cohort study.
Setting 24 towns in the United Kingdom.
Participants 6643 British men aged 40-59 years and free from cardiovascular disease at entry into the British regional heart study.
Main outcome measures Comparison of observed 10 year coronary heart disease mortality and event rates with predicted rates for each individual, using the relevant Framingham risk equation.
Results Of 6643 men, 2.8% (95% confidence interval 2.4% to 3.2%) died from coronary heart disease compared with 4.1% predicted (relative overestimation 47%, $P < 0.0001$). A fatal or non-fatal coronary heart disease event occurred in 10.2% (9.5% to 10.9%) of the men compared with 16.0% predicted (relative overestimation 57%, $P < 0.0001$). These relative degrees of overestimation were similar at all levels of coronary heart disease risk, so that overestimation of absolute risk was greatest for those at highest risk. A simple adjustment provided an improved level of accuracy. In a "high risk score" approach, most cases occur in the low risk group. In this case, 84% of the deaths from coronary heart disease and non-fatal events occurred in the 93% of men classified at low risk (<30% in 10 years) by the Framingham score.
Conclusion Guidelines for the primary prevention of coronary heart disease advocate offering preventive measures to individuals at high risk. Currently recommended risk scoring methods derived from the Framingham study significantly overestimate the absolute coronary risk assigned to individuals in the United Kingdom.

Introduction

The national service framework for coronary heart disease in England and Wales states that people whose estimated risk of coronary heart disease based on a specified risk factor profile is ≥30% over 10 years should be identified and offered appropriate advice and treatment.[1] European, American, and Canadian guidelines also use predicted 10 year risk to identify people for risk factor modification.[2–5]

It is recommended that risk assessment be performed using one of several methods that combine values for different risk factors to produce a