Aspirin for the prevention of cardiovascular disease: calculating benefit and harm in the individual patient

Yoon Kong Loke, Alastair Bell & Sheena Derry

Department of Clinical Pharmacology, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE

Aims To estimate the absolute reduction in the risk of cardiovascular events and absolute increase in gastrointestinal haemorrhage associated with aspirin for individuals with different baseline risks.

Methods Calculation of absolute treatment effects from estimates of: (i) baseline risks for cardiovascular event and gastrointestinal haemorrhage; and (ii) relative risks of these events with treatment. Baseline cardiovascular risks were derived from existing risk scores, and baseline risk of gastrointestinal haemorrhage from an observational cohort study. Changes in relative risks were obtained from clinical trial data. The effects of aspirin treatment were calculated in examples of two individuals with very different baseline risks.

Results Treatment of a healthy 74-year-old man (blood pressure 144/88 mm Hg and no history of gastrointestinal disorder) would reduce his annual risk of a cardiovascular event from 2% to 1.74% (absolute risk reduction 0.26%, number needed to treat 385), but increase the gastrointestinal haemorrhage risk from 0.3% to 0.51% (absolute risk increase 0.21%, number needed to harm 476). In a 66-year-old obese man, following a transient ischaemic attack, and with a history of hospital treatment for a peptic ulcer, the annual risk of a cardiovascular event would be reduced from 5% to 4.35% (absolute risk reduction 0.65%, number needed to treat 153), but the risk of gastrointestinal haemorrhage would increase from 1.08% to 1.83% (absolute risk increase 0.75%, number needed to harm 133).

Conclusions Estimating benefit and harm by taking into account the baseline risks in each individual allows patients and doctors to judge for themselves the magnitude of the trade-offs involved in taking aspirin.

Keywords: aspirin, benefit: harm analysis, cardiovascular event, gastrointestinal haemorrhage

Introduction

The antithrombotic action of aspirin was discovered in the 1960s, and aspirin is now widely used in the treatment and prevention of cardiovascular disease. It was first used for secondary prevention in patients with established disease, in whom the potential for benefit is reasonably clear. In recent years, however, there has been a tendency to use it for primary prevention of cardiovascular events in healthy patients, in whom the absolute level of benefit is much smaller. However, in some patients confounding factors increase the risk of adverse effects, such as gastrointestinal haemorrhage, to above average. The poten-

tial for harm in these patients may begin to outweigh that of benefit, and needs to be carefully evaluated in each case.

To illustrate this, it is helpful to consider two examples:

Case 1

A 74-year-old man presents to his GP with a blood pressure of 144/88 mm Hg, favourable cholesterol profile, and no other cardiovascular risk factors. His brother recently attended hospital with chest pain, and was given aspirin. He wonders if he too should take aspirin, given recent concerns about its gastrointestinal toxicity.

Case 2

An obese 66-year-old man with a blood pressure of 140/85 mm Hg has a transient ischaemic attack. Aspirin ther-

Correspondence: Dr Y. Loke, Department of Clinical Pharmacology, University of Oxford, Radcliffe Infirmary, Oxford OX2 6HE, UK. Tel.: + 44 1865 224524; Fax: + 44 1865 791712; E-mail: yoon.loke@clinpharm.ox.ac.uk

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apy is planned, but he was admitted to hospital 6 months before with a gastrointestinal haemorrhage. Peptic ulcer was diagnosed and he was given a proton pump inhibitor.

These cases pose the same difficult therapeutic dilemma: will aspirin's propensity for causing gastrointestinal haemorrhage be outweighed by the benefit of cardiovascular events prevented? In reaching a decision, it would be very helpful for the doctor and patient if the anticipated degrees of benefit and harm could be judged on an individual basis. We shall illustrate how an evidence-based approach can be used in this benefit : harm assessment.

Methods

Our main objective is to compare the absolute reduction in the number of cardiovascular events (stroke, myocardial infarction, or vascular death) with the absolute increase in the number of episodes of gastrointestinal haemorrhage with aspirin. For a particular individual we can calculate the absolute benefit or harm as a product of the treatment effects and baseline risks using methods described by Glasziou & Irwig [1]. The steps involved are summarized below:

- 1 Estimate the change in the relative risk of an event due to treatment, using the results of the clinical trials or meta-analyses that are most relevant to the patient's condition.
- 2 Estimate the baseline rates of cardiovascular events and gastrointestinal haemorrhage appropriate to the individual from risk tables and observational studies.
- 3 Multiply 1 (the relative risk) and 2 (the baseline risk) above to generate the on-treatment event rate, and compare it with the baseline rate. This allows us to calculate the number of events prevented or caused by the therapy.

In order for the above analysis to be valid, the underlying estimates on the treatment effects and baseline risks should be relevant and of good quality. The data sources we selected were full papers published in peer-reviewed journals with high impact factors.

The most applicable estimate of treatment benefit in Case 1 comes from a systematic review of four randomized controlled trials of aspirin in the primary prevention of cardiovascular disease [2]. For Case 2, the relevant figures can be obtained from a meta-analysis of aspirin treatment following transient ischaemic attack/ or non-disabling stroke [3, 4]. The best evidence for change in the relative risk of gastrointestinal haemorrhage associated with aspirin comes from a meta-analysis of randomized controlled trials of aspirin as an antiplatelet agent [5]. We checked these meta-analyses to confirm that the relative risk estimates for vascular events and gastrointestinal

haemorrhages were applicable across a spectrum of trials and patients. For other therapeutic problems estimates of relative risk should be taken from studies of specific relevance to that area.

The estimation of baseline cardiovascular risk can be obtained from charts, such as the New Zealand cardiovascular risk tables [6], or through a computer program [7]. Both are based on multivariate analysis of the major cardiovascular risk factors found in a North American population. There are now a number of studies that have demonstrated the applicability of such a model to northern European populations [8, 9].

A similar multivariate analysis for predicting gastrointestinal haemorrhage is not possible from current evidence. However, we were able to identify a prospective cohort study from which the major risk factors could be identified and their effects on the baseline risk of haemorrhage quantified [10]. This cohort consisted of residents in Tayside, Scotland who were aged 50 years and above. Age, past or present use of an ulcer-healing drug, and a history of hospital admission for any upper gastrointestinal event were the main factors assessed in the cohort. Univariate analysis of each factor gave a baseline risk for gastrointestinal haemorrhage, and in our analysis we used the highest baseline risk suggested by the risk factor profile. We performed our calculations on the basis of there being no evidence of an independent relationship between cardiovascular risk level and gastrointestinal haemorrhage.

It is worth stating, however, that the outcome measures in this cohort were 'complicated events', defined as gastrointestinal haemorrhage or perforation requiring admission to hospital, while the meta-analysis refers to the relative risk of gastrointestinal haemorrhage. Nevertheless, the vast majority (94%) of the 'complicated gastrointestinal events' recorded in the Tayside cohort were haemorrhages, and so the rate of haemorrhage reported in that study very closely reflects the baseline haemorrhage rate.

Results

Aspirin therapy has a relative risk of 0.87 (95% confidence intervals 0.81, 0.95) for vascular events in primary prevention [2], and 0.87 (95% confidence intervals 0.79, 0.96) following transient ischaemic attack or non-disabling stroke [3, 4]. For the purposes of this study we used the value of 0.87 with the wider confidence intervals of 0.79, 0.96. We applied this relative risk to different degrees of baseline cardiovascular risk, in order to calculate the number of events saved by aspirin therapy (Table 1).

The relative risk of gastrointestinal haemorrhage is increased during aspirin therapy to 1.69 (95% confidence intervals 1.51, 1.88) [4]. This figure was applied to the

Risk factor	Events per 10 000 per year (95% confidence interval)		
	Baseline	With aspirin	Change with aspirin
<i>Annual cardiovascular risk (%)*</i>			
1	100	87 (81, 95)	-13 (-5, -19)
2	200	174 (162, 190)	-26 (-10, -38)
3	300	261 (243, 285)	-39 (-15, -57)
4	400	348 (324, 380)	-52 (-20, -76)
5	500	435 (405, 475)	-65 (-25, -95)
6	600	522 (486, 570)	-78 (-30, -114)
<i>Risk factor for gastrointestinal haemorrhage</i>			
<i>Age of patient (years)</i>			
50-59	13	22 (20, 24)	9 (7, 11)
60-69	20	34 (30, 38)	14 (10, 18)
70-79	30	51 (46, 57)	21 (16, 27)
80-89	45	76 (68, 85)	31 (23, 40)
> 90	49	84 (75, 93)	35 (25, 44)
<i>Gastrointestinal history**</i>			
Ulcer drug use	42	71 (63, 79)	29 (21, 37)
Hospital admission	62	105 (94, 117)	43 (32, 55)
Ulcer drug use and hospital admission	108	183 (163, 203)	75 (55, 95)

*The cardiovascular risk of a patient can be derived using cardiovascular risk tables [5], or risk prediction computer programs [6]. **Past history of admission for any upper gastrointestinal event. Ulcer drug use is any past or present ulcer therapy.

different degrees of baseline risk for gastrointestinal haemorrhage associated with the identified risk factors, in order to calculate the number of events caused by aspirin therapy (Table 1, and Figures 1, 2 and 3).

Case 1

The 5-year cardiovascular risk is estimated from the risk tables [6] to be about 10%, giving an annual risk of 2%. From Table 1 we see that aspirin would be expected to save 26 (95% confidence interval 10, 38) cardiovascular events per 10 000 similar patients treated per year. Equally, for a 74-year-old man, aspirin would be expected to cause 21 (95% confidence interval 16, 27) gastrointestinal haemorrhages per 10 000 treated per year (Figure 2). Aspirin therapy for 1 year in patients with this risk profile would have a number needed to treat of 385 (95% confidence interval 263, 1000) to prevent one cardiovascular event, and number needed to harm of 476 (95% confidence interval 370, 625) to cause one additional gastrointestinal haemorrhage.

Case 2

The 5-year cardiovascular risk for a patient with symptomatic cardiovascular disease is above 20%, and in view of the patient's obesity, is increased by one further category to about 25% over 5 years [6]. Based on an annual risk of 5%, we expect aspirin to save 65 (95% confidence

interval 30, 114) cardiovascular events per 10 000 treated per year. In the absence of any gastrointestinal risk factors, the number of events prevented by aspirin therapy would be expected to greatly outweigh the number of gastrointestinal haemorrhages. However, the patient also has a history of admission to hospital for an upper gastrointestinal event, and the use of an ulcer-healing drug. This gives a risk of further bleeding with aspirin of 75 (95% confidence interval 55, 95) events per 10 000 treated per year, and makes the decision to treat less certain (Figure 3). In this case, the annual number needed to treat to prevent one cardiovascular event would be 153 (95% confidence interval 87, 333), with a corresponding number needed to harm of 133 (95% confidence interval 105, 182) to cause one additional gastrointestinal haemorrhage.

By using Figures 2 and 3, we can easily assess any changes in benefit : harm ratio that arise from variations in the baseline risk profile. For example, if the 74-year-old man (Case I) had previously been admitted to hospital with a peptic ulcer, then the increased absolute risk of gastrointestinal haemorrhages (75 per 10 000 treated per year) with aspirin would be expected to greatly outweigh the cardiovascular events prevented (26 per 10 000 treated per year). In this case, the annual number needed to treat to prevent one cardiovascular event would be 385, with a corresponding number needed to harm of 133 to cause one additional gastrointestinal haemorrhage.

Table 1 Number of events saved and caused by aspirin according to the baseline risk predicted by risk factors.

Figure 1 The number of gastrointestinal haemorrhages caused with aspirin therapy (per 10 000 treated per year) according to age, and past history of gastrointestinal disorder. Hospital admission is previous admission for any upper gastrointestinal event. Ulcer drug use is any past or present ulcer therapy.

Figure 2 Benefit : harm analysis of Case 1. The number of cardiovascular events saved with aspirin therapy plotted against the baseline risk of cardiovascular events, and the number of gastrointestinal events caused for groups of different baseline risks of gastrointestinal haemorrhage. The annual cardiovascular risk is 2%, meaning that 26 events per 10 000 treated per year are saved by aspirin. The risk of gastrointestinal haemorrhage is 21 per 10 000 treated per year.

Figure 3 Benefit : harm analysis of Case 2. The number of cardiovascular events saved with aspirin therapy plotted against the baseline risk of cardiovascular events, and the number of gastrointestinal events caused for groups of different baseline risks of gastrointestinal haemorrhage. The annual cardiovascular risk is 5%, meaning that 65 events per 10 000 treated per year are saved by aspirin. The risk of gastrointestinal haemorrhage is 75 per 10 000 treated per year.

Discussion

Our benefit-harm analysis of aspirin therapy allows us to quantify the reduction in cardiovascular events and the increase in gastrointestinal haemorrhage in an individual patient, according to the individual risk profile. This is in contrast to previous studies that have, for the sake of simplicity, attributed a constant haemorrhagic risk across the spectrum of patients [11]. Our tables extend this work and, in view of the millions of people for whom aspirin may be indicated, provide important information for: (i) those who are considering prescribing or taking aspirin; (ii) patients who are already taking aspirin, so that they can be fully informed of its likely effects; and (iii) policy-makers involved in drawing up guidelines or making recommendations on antiplatelet drug therapy.

The final step and the most difficult part of the analysis, that of balancing the relative impact of expected benefit and harm, remains to be considered. Cardiovascular events cannot be equated with gastrointestinal

haemorrhages on a simple numerical basis, as the range of severity for each type of event is considerable. There are also substantial variations among individual patients in the thresholds of acceptability for these treatment trade-offs, which make it impossible to assign definitive values to particular harms or benefits. The main determining factors here will be the patients' personal preferences, together with the advice of their own physicians [12]. Our analysis does not detract from the individual patient's role in this decision-making process, but supports it by providing robust evidence on which they can base their decision.

The scope of the therapeutic decision-making process can also be usefully extended with this benefit : harm assessment. Alternative strategies could be devised to reduce the risk of gastrointestinal haemorrhage in those who judge the trade-off to be unacceptable. For instance, there are observational data suggesting that prophylactic use of proton pump inhibitors could reduce the relative risk of haemorrhage by 40% [13]. Another option would be to use clopidogrel, which has similar antiplatelet properties, but a slightly lower rate of gastrointestinal haemorrhage compared with aspirin [14]. The relative risk reductions available with either strategy could easily be applied to the on-treatment event rate, to see if the trade-off for that individual becomes more acceptable.

While the advantages for clinical decision-making of quantifying benefit and harm are clear, some qualification of the present analysis is required.

The 95% confidence intervals for the number needed to treat and the number needed to harm are wide and they overlap, indicating that the benefit : harm ratio of aspirin treatment for patients may actually range from highly beneficial to quite unfavourable. This reflects the reality of clinical practice where it is impossible to say with any certainty which particular individuals will definitely have their stroke prevented, or which specific patients will suffer gastrointestinal haemorrhages.

Although gastrointestinal haemorrhage is the most common serious adverse event, aspirin can also cause haemorrhagic stroke. For the sake of simplicity we did not include the impact of aspirin on haemorrhagic stroke in our analysis. In any case, the risk is very small in absolute terms compared with that of gastrointestinal haemorrhage [15]. If it had been included, the attractiveness of aspirin therapy would have been reduced further, because, although the risk of haemorrhagic stroke is low, it carries a higher mortality. We have also not analysed other possible effects of aspirin, such as reduction in colonic cancer, or risk of allergic reactions, as the magnitude of these would be relatively small when compared with the main effects.

In calculating the harm associated with aspirin therapy we have emphasized the difficulty in predicting the base-

line risk of gastrointestinal haemorrhage. While our analysis took into account the effects of three major risk factors (age, a history of a gastrointestinal event, and prior ulcer drug therapy) a multivariate analysis of the risk factors was not possible. The risk of gastrointestinal haemorrhage in different age groups may be altered by the inability to separate those patients with a history of haemorrhage or ulcer drug therapy. However, as these patients formed only a small proportion of all the patients in the cohort, the age-related baseline risks quoted would not have been greatly skewed.

Furthermore, there may also be other risk factors that we have not been able to analyse in this observational cohort. We do not have any information on the use of aspirin or other nonprescription analgesics, or the use of anticoagulants or alcohol. All of these may have caused an overestimate of the baseline risk of haemorrhage. On the other hand, there may have been other confounding factors of which we are unaware (such as patients with haemorrhage not seeking hospital treatment), which may have predisposed to an underestimate.

These limitations are inherent in population-based observational studies. However, in the current absence of better data we believe that our analysis will be very useful to individual patients and doctors who want to weigh up the magnitude of benefit and harm associated with aspirin therapy.

In conclusion, considering the numerical benefit : harm ratio in two case scenarios illustrates the importance of incorporating individual baseline risks when quantifying the benefit and harm of aspirin. The use of a graphical technique incorporating these baseline risks enables doctors and patients to assess easily the benefit : harm ratio of aspirin in a particular individual.

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