Current perspectives

Low-dose aspirin in the primary prevention of cardiovascular disease: how to balance the benefits and the risks

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The favorable clinical experience with aspirin in the secondary prevention of cardiovascular disease, which has now clearly established the indications for the use of the drug in this context, has been the driving force behind the extension of its use to primary prevention. Here, however, the balance between the benefits and risks is substantially different from that of secondary prevention. In view of this, health authorities have been more reluctant to approve the generalized use of aspirin in primary prevention. We will here review the reasoning which should be at the basis of a set of recommendations, as recently expressed by two American expert opinion panels.

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Introduction

The extension of the use of aspirin from the secondary to the primary prevention of cardiovascular disease is based, in principle, on the favorable clinical experience in secondary prevention (reviewed from the Antiplatelet Trialists' Collaboration[1,2]), which has now clearly established the indications for the use of the drug in this context. However, in primary prevention the balance between the benefits and risks is substantially different from what occurs in secondary prevention. In view of this, health authorities have been more reluctant to approve the generalized use of aspirin in primary prevention. This short paper aims at reviewing the reasoning behind this and hopes to explain the recent position of the American Health Authorities, recently expressed in two expert opinion panels[3,4]. This may serve as a guide to issue recommendations on the use of aspirin in the primary prevention of cardiovascular diseases.

The benefits of aspirin in primary prevention

In studies with aspirin in various groups of subjects and various types of indications, the reduction in the relative risk of cardiovascular events appears constant, around a mean of about 30%[1,2,5]. This means that the absolute reduction of events is nearly a linear function of the absolute risk (Fig. 1)[6]. Thus, the benefits of aspirin in a situation at very high cardiovascular risk, such as unstable angina (in which 15% of subjects treated with placebo have a major vascular event within 1 year), is more evident – and much easier to demonstrate in a trial – than in subjects with chronic stable angina (in which only 4% of subjects have a major vascular event within 1 year). These differences in efficacy are now commonly indicated with the *number needed to treat* (NNT), i.e. the number of subjects that need to be treated for 1 year to avoid one major vascular event, which is the inverse of the absolute risk reduction. If aspirin reduces the risk of myocardial infarction by 30% at 1 year in a situation such as unstable angina (absolute risk on placebo 0.15/year), the absolute risk reduction will be 0.045/year, and the NNT is 22.2. In a situation like chronic stable angina (absolute risk on placebo 0.04/year), with the same relative risk reduction, the absolute risk reduction will be lower, namely 0.012/year, and the NNT correspondently higher, namely 83. Moving towards categories of progressively lower risk, the NNT to avoid a major vascular event progressively increases, and the treatment becomes less and less "efficient" in reducing the number of events in the same number of patients. These are considerations which are useful for an understanding of the benefits of aspirin in various clinical situations.

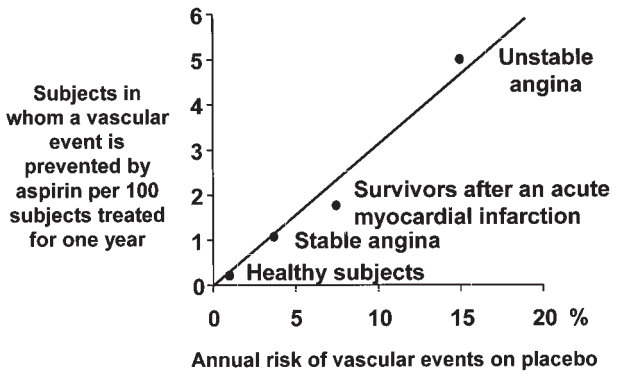

Figure 1. *The relationship between the level of benefit of aspirin* (on the ordinate) *as a function of the absolute level of cardiovascular risk in various categories of subjects* (on the abscissa). *From Patrono et al.[6], modified.*

The risks

The use of aspirin involves a hemorrhagic risk. This is in part due to the gastrointestinal (GI) toxicity which increases linearly with the dose (antirheumatic doses of aspirin have a notoriously higher GI toxicity than the low doses more widely prescribed for antithrombotic prophylaxis), but that partially depends on the inhibition of platelet function (which is therefore intimately related to the antithrombotic effect of aspirin), and reaches a plateau for doses in the order of 50-100 mg/day (the so-called "low doses") upon repeated administration.

Controlled trials in primary and secondary prevention settings also suggest that aspirin slightly increases the rates of hemorrhagic strokes (0 to 2 per 1000 persons given aspirin for 5 years)[3]. Such estimates are less reliable than those of GI bleeding because only a few strokes were reported in the trials.

The hemorrhagic risk of aspirin does *not* depend on the level of cardiovascular risk, and is estimated at around a relative risk of 1.77. This means: slightly less than a doubling of the baseline risk of major bleeding in a population of subjects who are untreated or treated with placebo, where the risk is estimated at 0.22 major episodes of bleeding per 100 subjects/year in an untreated population[7,8]. The excess risk of major bleeding attributable to aspirin is therefore set at around 0.17/100 subjects treated/year.

Assessing the benefit/risk ratio

The risk of bleeding due to aspirin is clearly more than offset by its benefits in preventing major vascular events in situations at high cardiovascular risk, such as those investigated in secondary prevention trials. But what happens when we take populations at lower risk into consideration?

The dependence of the cardiovascular benefits of aspirin (number of cardiovascular events avoided) on the level of risk of the population on the one hand and, conversely, their independence from the number of major bleedings (mostly GI), can be represented together (Fig. 2)[9-14]. The lines depicting the two independent trends, one – the benefit – depending on the cardiovascular risk of the population, the other – the hemorrhagic risk – independent of the cardiovascular risk of the population, intersect at a level of risk in the population approximating 1.0 cardiovascular event per 100 patients/year. Above this value, the number of cardiovas-

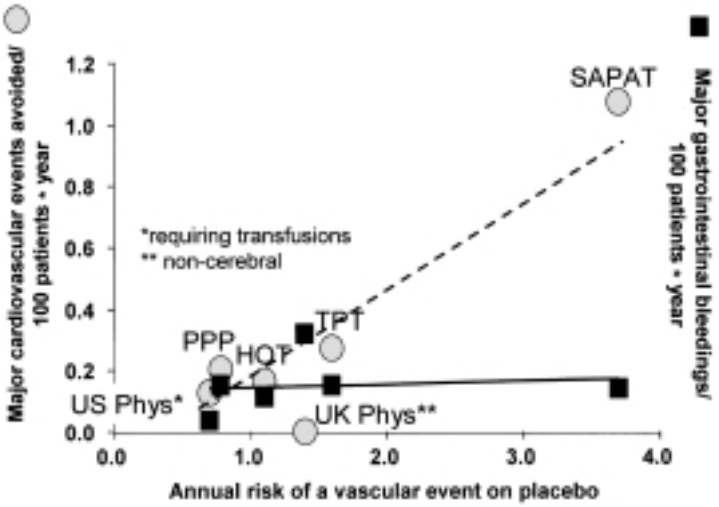

Figure 2. *The relationship between the level of benefit of aspirin* (on the ordinate) *as a function of the absolute level of cardiovascular risk in various categories of subjects in primary prevention* (on the abscissa) (broken line). *Data are derived, just as in figure 1, from the main studies reported so far: US Phys[12], UK Phys[13], Thrombosis Prevention Trial (TPT)[10], HOT Study[11], Primary Prevention Project (PPP)[9]. The datum of the SAPAT study[14] regarding the use of aspirin in stable angina is also included. The risk of major gastrointestinal hemorrhagic events (requiring transfusions) in the various studies* (continuous line), *which – as shown in the figure – is independent of the level of cardiovascular risk, can be used to calculate a threshold value for cardiovascular risk, below which the use of aspirin in primary prevention becomes unattractive because it is associated with a quite uncertain, if not clearly unfavorable, benefit/risk ratio. Data kindly provided by Dr. Marchioli.*

cular events avoided clearly outweighs the number of bleedings induced.

However, below such a value, aspirin appears to induce more bleedings than the cardiovascular events avoided. As can be seen from figure 2, the population in a recent large primary prevention study, the Primary Prevention Project (PPP)[9], is at a level of risk below 1.0 cardiovascular event per 100 patients/year. According to this line of reasoning, therefore, in a population similar to that of the PPP (primary prevention in subjects with only one major cardiovascular risk factor) in partial contrast with the very same conclusions of the study, aspirin should probably not be prescribed. In the PPP the authors note that only one fatal bleeding complication occurred, and that there were no suggestions of an excess risk of intracranial hemorrhages in the 8000 subjects/year undergoing aspirin treatment. Our reasoning is however based on a composite analysis of the results of all primary prevention studies, and concludes with a note of caution on the widespread applicability of aspirin indications in these situations. As a matter of fact, in the PPP there were 24 episodes of bleeding in the group assigned to aspirin as compared to 6 such episodes in the control group. There were 2 intracranial (non-intraparenchymal) hemorrhages in the aspirin group and 0 in the placebo group.

Assumptions and limitations

This reasoning makes a number of assumptions that also merit further discussion:

• a major cardiovascular event is weighed as equal, in terms of clinical relevance, to an episode of major bleeding necessitating transfusion. One might argue that a patient might "prefer" to go through (or a doctor might prefer his patient to go through) an episode of bleeding rather than a myocardial infarction; part of these bleedings are however cerebral hemorrhages, and the even modest excess of such a devastating and invalidating side effect observed in the aspirin studies as a whole imposes some caution in generalizing the advice of administering aspirin to anyone. In this case the principle of *primum non nocere* has to prevail;

• risk estimates are probabilistic, and one should always quote and show the confidence intervals of the measure. These would certainly give a good idea of the uncertainty of our measurements. Confidence intervals are reported in the table of recommendations from the recent US Preventive Services Task Force[3];

• the assumption of a linearity in the reduction of events with aspirin as a function of the level of cardiovascular risk is in agreement with the data obtainable from the various studies available (Fig. 1), but does not exclude curvilinear models. A linear model implies that the contribution of platelet aggregation in cardiovascular events is the same regardless of the condition of risk. As an example, it would imply that the myocardial infarction occurring in a previously healthy population has the same platelet contribution as the infarction in unstable angina. This is likely, but has not yet been completely demonstrated. If the model were non-linear, the estimates of the "threshold" level of risk, below which the use of aspirin would become non-advantageous, would be burdened with further uncertainty;

• the assumptions on the bleeding risk estimated in this analysis are mediated from a large body of data in large-size clinical trials. These estimates are approximate, being average values, and could be much higher in particular categories, such as the elderly, or in patients submitted to a simultaneous treatment with non-steroidal anti-inflammatory drugs.

How to transfer these results to everyday clinical practice?

We cannot oversimplify and state that, in primary prevention, a subject at high risk should be given aspirin and a subject at low risk should not, because a large "grey area" that is not addressed by the oversimplification would still remain. The Thrombosis Prevention Trial[10] and the HOT trial[11] have demonstrated advantages from the use of aspirin, while this was not so obvious in the Physicians' Health Study[12] and the British Doctors' Trial[13], and is debatable, for the reasons highlighted above, in the most recent PPP[9]. The solution to this *vexata quaestio* is in an estimate as accurate as possible of the cardiovascular risk in primary prevention. For this reason, one may use, for the European population, the tables reported by the Second Joint Task Force of European and other Societies on coronary prevention, in a document endorsed by the European Society of Cardiology, the European Atherosclerosis Society, the European Society of Hypertension, the International Society of Behavioral Medicine, the European Society of General Practice/Family Medicine, and the European Heart Network[15].

On the basis of these tables, a 70-year-old hypertensive (systolic blood pressure of 160 mmHg), non-smoker, non-diabetic woman has an absolute risk of cardiovascular events below the cut-off level of 1%/year if her total cholesterol is < 175 mg/dl. On the contrary, a male subject with the same characteristics falls above such a threshold, and would therefore deserve treatment with aspirin. These estimates are important to push the doctor on the issues of the benefit/risk ratio of the treatment, and to sort out the patients at high risk in primary prevention. All this would always have to be pondered carefully together with the considerations that these are statistical estimates, useful to orient therapy in general, but which would never tell us if we will do good or bad in proposing or discouraging the use of aspirin in the single patient. I have used the words "proposing" and "discouraging" on purpose.

Table I. Estimates of benefits and harms of aspirin given for 10 years to 1000 persons with various levels of baseline risk for coronary heart disease (CHD).

	Baseline risk for CHD over 1 year		
	0.2%	0.6%	1%
Total mortality	No effect	No effect	No effect
No. CHD events	2-8 avoided	8-24 avoided	12-40 avoided
No. hemorrhagic strokes*	0-4 caused	0-4 caused	0-4 caused
No. major GI bleeding events**	4-8 caused	4-8 caused	4-8 caused

GI = gastrointestinal. * data from secondary prevention trials suggest that an increase in hemorrhagic stroke may be offset by a reduction in other types of stroke in patients at very high risk for cardiovascular disease (10% 5-year risk); ** rates may be 2 to 3 times higher in persons > 70 years of age. From US Preventive Services Task Force[3], modified.

Because, never as in this case, is it necessary to discuss the options with the patient so as to involve him in a certainly not trivial choice.

As the end-result of this reasoning, aspirin is, in our opinion, indicated for the prevention of myocardial infarction and other cardiovascular thrombotic events in persons at a higher cardiovascular risk, i.e. males and females (mostly over the age of 50 years) who have a cardiovascular risk of ≥ 1% per year.

These recommendations (cut-off values > 1.0 per 100 patients/year) are consistent with – but more conservative than – the cut-off values recommended by the recent US Preventive Services Task Force [*"Although the balance of benefits and harms is most favorable in high-risk persons, those with a 5-year risk ≥ 3%* (≥ 0.6 per 100 patients/year), *some persons at lower risk may consider the potential benefits of aspirin to outweigh the potential harms"*] (Table I)[3] and perfectly in line with the recent statement of the American Heart Association Consensus Panel [*"Therefore, consider 75-160 mg aspirin per day for persons at higher risk (especially those with a 10-year risk of coronary heart disease ≥ 10%")*] (≥ 1.0 per 100 patients/year)[4] (Table I).

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