

Discussion paper

Ethical considerations in relation to aspirin prophylaxis

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ABSTRACT

Low-dose aspirin prophylaxis, 75–150 mg per day, reduces the risk of vascular events and there is also promising evidence that it may also reduce the risk of cancer. Increased use of aspirin may confer considerable benefits to the population, but the risk of causing a gastric bleed is certainly a major concern. There are ethical considerations related to the potential increased use of aspirin in the population. These include the balance of benefit and risk of the medicine, possible undesirable effects such as ‘risk

compensation’ and ‘iatrogenesis’, as well as a potential impact on health inequalities. More research is therefore needed on aspirin, particularly to define and describe the population use of the drug. More evidence on aspirin, including an ongoing randomised controlled trial on vascular events, will allow appropriate policy responses to be made.

Keywords: aspirin, bleeding, cancer, ethics, policy, vascular events

How this fits in with quality in primary care

What do we know?

Aspirin is a medicine that is used in low doses for prophylaxis against vascular events. The medicine has undesirable effects and there is a balance between benefit and risk.

What does this paper add?

The ethical considerations surrounding aspirin prophylaxis are far-reaching and extend into complex psychosocial considerations. Numerous research directions are also identified, most notably on the use of aspirin in the population.

Introduction

Meta-analyses of randomised controlled trials (RCTs) provide evidence that low-dose aspirin prophylaxis, 75–150 mg per day, reduces the risk of death, myocardial infarction and ischaemic stroke in individuals with a high risk of vascular events.¹ High-risk individuals include those with a history of vascular events or with conditions associated with increased risk of occlusive vascular disease, such as angina pectoris.¹

A recently published report from the United States (US) evaluates preventive measures for vascular events, covering both lifestyle and pharmacological approaches. Aspirin prophylaxis in high-risk individuals was placed first in a list of the preventive activities of greatest benefit.² Furthermore, health economic studies provide

further support to the value of aspirin prophylaxis in reducing the risk of vascular events.^{3,4}

There is also highly promising, but not conclusive, evidence that aspirin may reduce the risk of developing cancer.⁵ Four RCTs, one using a low dose, show that aspirin reduces the risk of developing pathological changes associated with colorectal cancer. The limitation to the RCTs, however, is that they use a proxy outcome measure rather than cancer as the endpoint. The four aspirin RCTs that have measured cancer as the endpoint have used different dose and duration regimes and, perhaps not surprisingly, they show variation in results. The evidence suggests that daily aspirin use over 10 years might reduce the risk of

colorectal cancer, although further uncertainties remain over the optimum dose. On current evidence, firm policy recommendations on aspirin and cancer could therefore be premature. The emerging evidence on aspirin and cancer will be of interest to a number of organisations, including the National Screening Committee, given the recently introduced colorectal cancer screening programme in the UK.⁶

Aspirin is an inexpensive medicine that is easily available in the community, but more data are needed on the level of use in the population.^{7,8} Given the vascular benefits of aspirin, as well as the highly promising evidence of benefit against cancer, the appropriate increased use of aspirin might confer considerable benefits to the population.⁹ Vascular disease and cancer are significant causes of disease, disability and death in the population. On the other hand, some have stated that aspirin is not an ‘innocent medicine’,¹⁰ while others call the medicine a ‘poison’.¹¹

These different perceptions of aspirin are interesting. It is certainly reasonable to highlight the undesirable effects of aspirin. The risk of low-dose aspirin causing a gastric bleed is certainly a major concern. Both spontaneous bleeding and that attributable to aspirin increase with advancing age.¹² It may be very reasonably argued, however, that a gastric bleed is far less serious than a vascular event in terms of risk of death, consequences, effects on family and friends and the ongoing costs to health and social care services. Indeed, one model has suggested that low-dose aspirin at the age of 50 years of age only carries the same mortality risk as car driving.¹³ However, there are ethical considerations associated with aspirin and the potential increase in the use of the medicine in the population.

Ethical considerations

General principles

Four *prima facie* ethical principles have been suggested,¹⁴ namely:

- beneficence – literally, doing good
- non-maleficence – literally, not causing harm
- respect for persons – also acknowledges autonomy
- justice – implies equity or fairness.

Healthcare professionals are trained to ‘*first do no harm*’. In the case of aspirin, the medicine can cause harm and unfortunately this also raises the possibility of litigation if undesirable effects do occur. Furthermore, healthcare professionals are unable to predict the individual effect of aspirin; vascular events may still occur in some individuals taking the medicine. So

the assessment of the benefit versus risk balance may be different between healthcare professionals and individuals considering aspirin prophylaxis.

Balance of benefit and risk

The beneficence versus non-maleficence balance is one of the key ethical considerations that help inform recommendations on low-dose aspirin prophylaxis. Presented in Box 1 are some of the quantitative considerations associated with the balance of benefit and risk with aspirin, as well as some of the issues arising from this.

Areas of debate still remain on aspirin prophylaxis recommendations. For example, different recommendations have been made between USA and European scientific societies for individuals with type 2 diabetes mellitus.¹⁵ These different recommendations, which are drawn from the same evidence base, highlight the need for consistent recommendations on aspirin prophylaxis to be made a matter of urgency, in order to avoid ‘postcode prescribing’ at an international level.

Aspirin use on age grounds

The different recommendations also highlight the ongoing debate about which individuals should consider taking aspirin prophylaxis.¹⁶ This debate is intensified by the controversial proposal that aspirin might be taken on age grounds alone by individuals over the age of 50 years.¹⁶ The underlying basis for the proposal is robust, as the risk of vascular events increases with age. There is also evidence from population studies,¹⁷ but not RCTs, suggesting that many individuals by the age of 50 years have reached a level of vascular risk for which aspirin prophylaxis is an ethical option.

The use of aspirin on age grounds raises further ethical issues. For example, in order to respect individual autonomy, such decisions would appear to be best made by an individual if they were fully informed about the benefits and risks of taking aspirin. So should a health-education campaign on the effects of aspirin be conducted? This would at least allow informed choices to be made, although there might also be some unintended consequences, such as taking aspirin prophylaxis in preference to and at the exclusion of other measures which improve health, so-called ‘risk compensation’.

Risk compensation

In the theory of ‘risk compensation’, the perception of protection against an adverse outcome may lead to behaviours that constitute other risks. For example, circumcision of men reduces the risk of HIV infection, but this perceived protection might be a barrier to

Box 1 Quantitative considerations on the balance of benefit and risk

Preventing a first vascular event is often termed primary prevention, while secondary prevention refers to the prevention of a subsequent event. Although there are limitations to the dichotomy of primary and secondary prevention,¹⁶ in general, the terms may be considered to be proxy measures for vascular event risk. A meta-analysis of four primary prevention RCTs has provided valuable data on the relationship between vascular event risk and the beneficence versus non-maleficence balance of aspirin.¹⁸ The study only evaluated the relationship with respect to myocardial infarction, although the general principles also apply to ischaemic stroke, namely the greater the risk of a vascular event the stronger is the case for low-dose aspirin prophylaxis to be recommended, unless contraindications exist.

At a low risk of 0.5% per annum, that is five individuals per 1000 per annum experience a myocardial infarction, 133 individuals need to be treated for five years to avoid one myocardial infarction. In balance to this, the number needed to harm (NNH) from major bleeding attributable to aspirin was one individual for every 500 treated. With an increased risk of 1% per annum, the number of individuals needed to treat (NNT) to avoid one myocardial infarction was 67, and the NNT to prevent one myocardial infarction net of major bleeding was 182. The corresponding NNT figures at a high risk of 1.5% annum were 44 and 77 respectively. So at low 0.5% annual risk, the benefit versus risk balance of aspirin appears unfavourable, while at high 1.5% annual risk, aspirin appears safe and worthwhile. Of course, this evaluation is based only on numbers rather than taking account of the morbidity and mortality of the outcomes.

A meta-analysis of six secondary prevention RCTs offers further data on aspirin use in individuals at high risk of vascular events.¹⁹ In this meta-analysis, the risk of myocardial infarction was reduced by 26% (NNT = 83) and the corresponding figures for ischaemic stroke were 25% (NNT = 40) and for all-cause mortality 13% (NNT = 71) respectively. In balance to this, aspirin doubled the risk of experiencing severe bleeding, with a NNH of 111. This NNH is important because individuals in secondary prevention trials may have more risk factors for severe bleeding than those in primary prevention trials, for example older age and greater comorbidity. This also raises a more general point about NNT and NNH, namely that they are heavily dependent on the baseline characteristics of the population under study.

So what level of annual vascular event risk is appropriate for aspirin prophylaxis? Most importantly, who judges this risk level? Is it the responsibility of a committee to provide evidence-based recommendations? Alternatively, is it for a clinician to judge, based on a formal estimation with an individual of their annual vascular event risk? Or should it be an individual decision, based on an informed choice on the benefits and risks of aspirin and taking into account personal health values? It is important to differentiate between disease treatment in which a clinician assumes a major role, and preservation of health in which individual autonomy should not be compromised.²⁰

Of further relevance is the possibility of aspirin resistance.²¹ It has been estimated that about one-quarter of individuals do not receive the vascular benefits from taking aspirin although they retain the risk of undesirable effects of the medicine. The beneficence versus non-maleficence balance in aspirin-resistant individuals is clearly unfavourable, and more work is needed on this important issue.²²

safer sexual practices.²³ Another example is whether larger four-wheel-drive cars lead to dangerous driving because their drivers feel safer,²⁴ although this point has been debated.²⁵ The concern, therefore, is that some individuals may choose to take an aspirin, because it is convenient to do so, at the exclusion of taking exercise, modifying their diet if required, and so on. An even worse possibility is that some individuals may either adopt or justify risky health behaviours, such as binge drinking alcohol or smoking, because they believe that their health is protected by aspirin. 'Risk compensation' might be a highly undesirable psychosocial consequence to a health-education campaign on aspirin, since the medicine is a complement rather than a competitor or alternative to other measures intended to improve population health. This last issue further raises the concept of utilitarian ethics.

Utilitarian versus rights-based ethics

A tension exists between efficiency to maximise health gain within available resources, and the need for equity, which relates to fairness.²⁶ Although increased aspirin use might benefit the population as a whole, individuals would be harmed. Is this fair to those individuals who are harmed? Is this fair to the population? To answer these questions requires a social value judgement, and this in turn balances two potentially conflicting ethical philosophies.²⁶ The first is utilitarianism in which the obligation is to produce the 'greatest good for the greatest number'. The second is a rights-based philosophy in which the individual is valued and not seen as a means to an end. The social value judgement on the increased use of aspirin raises a further fundamental question. Who decides if increased

aspirin use is good for society? This ethical question certainly deserves to be debated further.

Iatrogenesis

Increased use of aspirin might confer considerable direct and indirect benefits to the population. The direct benefit could arise from the reduced burden of vascular disease and possibly cancer. The indirect benefit may arise from releasing limited health and social care resources for use elsewhere. On the other hand, increasing aspirin use would lead to more undesirable effects, so-called 'iatrogenesis'. The concept of iatrogenesis was first put forward in 1974 by Ivan Illich,²⁷ and is based on the concept of nemesis, namely retribution as a backlash against the '*medicalisation of society*'. Increased aspirin use would certainly lead to medical iatrogenesis by causing more cases of bleeding. There may also be social iatrogenesis, due to increase in the 'sick role'.²⁸ Aspirin use might be disempowering for some individuals who may consider the taking of a medicine as evidence of being ill. Such disempowerment particularly applies to vulnerable groups in society who have diminished autonomy.

Respect for individuals

Respect for individuals also implies a moral requirement to protect those with diminished autonomy, such as vulnerable groups in the population. In the case of aspirin prophylaxis, information is widely given in newspapers and magazines, so-called lay epidemiology,²⁹ sometimes with widely different levels of accuracy.

Factors that underpin the decision of an individual as to whether or not to take aspirin may be explained, at least in part, by the health-belief model first described over 30 years ago.³⁰ The model attempts to explain and predict a given health-related behaviour from certain patterns of belief about the recommended behaviour and the health problems that the behaviour intends to prevent or control. One of the criticisms of the health-belief model is that the behaviour of an individual is assumed to be rational, which may not apply to some vulnerable groups. For example, some age-related mental health problems could compromise the ability of individuals to independently make appropriate decisions on aspirin prophylaxis.³¹ In addition, there may be sociological factors that influence the ability of some to make decisions on aspirin prophylaxis.

Sociological and psychological considerations

Medical sociology provides an important perspective in relation to ethical matters.³² Some individuals

taking low-dose aspirin may assume a 'sick role', particularly in those 'sick populations' with high disease incidence, poor internal bonds and high social dysfunction.³³ In these 'sick populations', especially in lower social classes, there are greater determinants of vascular disease and cancer, namely high levels of alcohol consumption and smoking, poor diet and low levels of exercise.^{34,35} Increased aspirin use could have most benefit in these 'sick populations' were it not for another dimension. Inequalities in health result fundamentally from inequalities in wealth.³⁶ The potential benefit of aspirin therefore needs to be considered as part of a wider sociological context. Psychological models, such as Maslow's hierarchy of needs,³⁷ are helpful to prioritise issues within a 'sick population'. Indeed, in these populations, there may be psychosocial constraints that undermine some individuals' fulfilment of their potential or 'self actualisation'.³⁷ In such individuals, aspirin prophylaxis may not be as much of a priority as 'basic needs', for example employment. Psychosocial constraints may therefore impede lifestyle change. Understanding disease trends in the population also helps provide evidence to inform policy development.

Disease trends

Between 1981 and 2000, the mortality rate from vascular disease in England and Wales fell by 54%.³⁸ One important reason for this fall has been the reduction in exposure to major risk factors, such as smoking, which fell by about one-third during this period.³⁹ Effective treatment of disease, such as high blood pressure, is another key factor for the fall in mortality rate from vascular disease.³⁹ This trend is one of the main reasons why life expectancy is increasing in the UK, the so-called 'age cohort effect'.

These trends raise another fundamental question. Is it ethical to even consider increased aspirin use? Since 1981, there have been reductions in both the determinants, such as smoking, as well as the predictors, such as levels of high blood pressure, of vascular disease within the population. Introducing a policy to increase aspirin prophylaxis might not be necessary given these trends and the possible undesirable consequences described previously. However, vascular disease is still a major issue in terms of premature and preventable deaths. Another consideration is the increase in risk associated with type 2 diabetes mellitus and obesity among young adults aged 35–44 years.⁴⁰ Furthermore, childhood obesity has been described as a '*looming crisis*', especially given that obese children tend to be heavy in adulthood.⁴¹ Given the observations in 35–44 year olds, the declining trends reported for vascular disease deaths may slow or reverse in future, perhaps aspirin policies might help maintain the current

declining trend. Aspirin may also be part of a wider strategy, for example anti-obesity measures range from lifestyle approaches to over-the-counter orlistat, a drug which reduces dietary fat absorption.⁴² This wider health agenda further raises ethical issues related to possible increased aspirin use.

The wider agenda of health

There are non-modifiable and modifiable determinants of disease. The former includes age, sex and genetic predisposition. For example, ageing is a very important determinant of vascular event risk, since more than 75% of all heart attacks and ischaemic strokes occur in people over the age of 65 years.⁴³ Sex is important, for example there is suggestive evidence that women might be more susceptible to developing smoking-related illnesses compared with men.⁴⁴ Genetic predisposition is also a key non-modifiable risk factor, and 'Mendelian randomisation'⁴⁵ suggests that individuals with a genetic variation that mimics the effects of aspirin have reduced risks of colorectal cancer.⁴⁶

There are also modifiable risk factors for disease. In both sexes, absence of smoking, body mass index (BMI) of below 25 kg/m², physical activity of at least 30 minutes per day, at least half a unit of alcohol per day, and low salt diets or increased fruits, vegetables, cereal fibre and polyunsaturated fatty acids (PUFAs) appear to lower disease risk.^{47–50} Aspirin prophylaxis has the potential to complement these other lifestyle approaches to lower disease risk. Any suggestion that aspirin is an alternative to addressing modifiable disease determinants would be unreasonable and unethical. This raises another issue of possible complements to low-dose aspirin prophylaxis for improving the health of the population.

Complements to aspirin

The question '*Are statins the next aspirin?*' has been posed because of evidence that statins may lower cancer risk.⁵¹ Indeed, parallels exist between aspirin and statins; simvastatin is also available over the counter,⁵² and there is the potential to increase statin use in patients at high risk of vascular events.⁵³ There are two reasons why these comparisons are unhelpful. Firstly, aspirin costs substantially less than other drugs used for vascular disease prophylaxis, with aspirin less than one-fifth the cost of statins.⁵⁴ Secondly, aspirin should not be regarded as an alternative to other drugs, and if the vascular event risk of an individual is estimated to be greater than 3% in five years, then the addition of a statin should be considered.⁵⁵

The 'polypill' is a proposal to combine a statin, three blood pressure-lowering drugs, folic acid and low-dose aspirin into a single tablet.⁵⁶ It has been claimed that the 'polypill' could reduce vascular disease by 80%, although doubts about cost-effectiveness remain.⁵⁷ Others have rejected the pharmaceutical approach and have proposed a 'polymeal' rather than a 'polypill', which includes wine, fish, dark chocolate, fruits, vegetables, garlic and almonds.⁵⁸ Based on life tables from the Framingham cohort study, the 'polymeal' might reduce the risk of vascular disease by more than 75%. However, instead of considering either a 'polypill' or 'polymeal', perhaps we should be considering 'poly-lifestyle'. A cohort study of 20 000 men and women aged 45–79 years in east England found that regular exercise, 1–14 units of alcohol per week (1 unit = glass of wine or half pint of beer), eating five servings of fruits and vegetables per day, and not smoking could prolong life by 14 years.⁵⁹ So in accordance with the concept of 'iatrogenesis', is it ethical to medicalise health given that there appear to be effective lifestyle approaches to reduce disease risk? Health inequalities are also important.

Impact of aspirin on inequalities

The socio-economic gradient of health experience is well described. Men in the lowest social classes have twice the mortality rate of men in the highest social class. This has been attributed to differences in the way members of social classes lead their lives.⁶⁰ One study on inequalities reported that disadvantage such as poor-quality housing, exposure to environmental pollution in area of residence, occupational hazards, poor diet, smoking, risk of unemployment and low income were most concentrated in the lowest social class, diminishing for each step up the social hierarchy.⁶¹

The highest life expectancy is found in the most-affluent groups, which suggests that geographical variation in life expectancy can be largely explained by socio-economic deprivation.⁶² These considerations of inequality are of relevance to the potential wider use of aspirin and raise another question. Is it ethical to promote aspirin in areas of deprivation more intensively than in affluent areas? In accordance with the 'inverse care law',⁶³ individuals in the lowest social classes have the lowest uptake of preventive care,⁶⁴ with the possibility that increased aspirin use in the population could lead to greater use in affluent compared with disadvantaged areas. Increased aspirin use could lead to widening health inequalities. There is also a wider debate about health, given that several models exist, including the medical model, health-promotion model and sociological model.

What next for aspirin?

From an ethical perspective there are reasons for and against increasing the use of prophylactic low-dose aspirin in the population. The need for further debate calls into question whether it is time for another aspirin conference to be convened.⁶⁵

Policy proposals for aspirin have been put forward, including promoting its use in individuals at high risk of vascular events, using the General Medical Service (GMS) contract,⁶⁶ and a population-based health-education campaign to allow informed choices on use to be made.⁶⁷ These policy proposals may be considered part of a co-ordinated vascular disease-prevention programme, applicable to individuals and populations and amenable to evaluation.⁶⁸

In addition to vascular disease-prevention programmes, the growing evidence on aspirin and cancer might also be relevant to the development of future aspirin policies. With the limitations to evidence-based policy,^{69,70} the emphasis should be more on evidence-informed policy.⁷¹ However, because of uncertainty of impact from increased aspirin use, the ethical precautionary principle might be invoked.⁷² Put succinctly, the precautionary principle is 'better safe than sorry', which argues for ethical resistance to policy development and change in use of aspirin. The precautionary principle, it has been suggested, takes a view based on pessimism rather than an objective evaluation of costs and benefit.⁷³

So what happens next? The potential of aspirin to improve the health of the population does deserve to be given serious consideration. In accordance with the 'Rose prevention paradox',⁷⁴ the large number of individuals who are exposed to an intervention which reduces risk of disease may confer considerable population benefit.⁷⁵ Others, however, have commented that health is already being redistributed pharmacologically in the population by statins, antihypertensive drugs and nicotine-replacement therapy,⁷⁶ so is the increased use of another medicine ethical?

Inaction on aspirin prophylaxis does not seem to be a reasonable or ethical option. One of reasons why action is required is because media reports are increasingly bringing the potential of aspirin to the attention of the general public, especially in terms of possible reduction in the risk of cancer. The role of the media in reporting medical news stories is sometimes unbalanced,⁷⁷ which could lead to inappropriate use of aspirin. While acknowledging the ethical complexity of increased aspirin use, there are currently significant gaps in knowledge which would compromise any policy development. Research is needed as a matter of urgency, in order to define and describe the population use of aspirin, the benefits and harms caused, the reasons for aspirin use and whether it should be

considered part of a holistic approach to improving health. For example, in the Medical Research Council Cognitive Function and Ageing Study which includes approximately 13 000 individuals aged 65 years and over from England and Wales,⁷⁸ there appears to be a correlation between 'self-perceived health' and life expectancy, although the effect of aspirin on psychosocial dimensions of health is not known. Research needs to focus on ways to minimise the undesirable effects of aspirin in order to fully maximise the possible beneficence versus non-maleficence balance.⁷⁹

More evidence on aspirin will be forthcoming in future. For example, Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) is an RCT including 12 000 individuals in 400 centres in Germany, Italy, Spain, UK and USA. The study involves men aged over 50 years with at least two of the following risk factors – smoking, family history of heart disease, high blood pressure or high cholesterol – and women, aged over 60 years with at least three risk factors. This trial is under way and reports in 2013. Given that the population is ageing,⁸⁰ there is an ethical responsibility to ensure that gaps in knowledge on aspirin are filled, allowing appropriate policy on aspirin to be implemented and modified to embrace new evidence when it becomes available.⁸¹ Such policies may have far-reaching implications for the health of the population and the delivery of primary care services, by contributing to the increasing focus on the vascular disease-prevention agenda. However, the ethical question of the balance between prevention and treatment will also need to be considered.⁸²

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CONFLICTS OF INTEREST

None.

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