Use and Misuse of Aspirin in Primary Cardiovascular Prevention

Sergio Coccheri

School of Medicine, University of Bologna, Bologna, Italy.

Clinical Medicine Insights: Cardiology
Volume 11: 1–4

DOI: 10.1177/1179546817702149

SAGE

ABSTRACT: The use of low-dose aspirin in primary prevention of cardiovascular (CV) events in healthy or apparently healthy people is a widely debated topic. Many arguments indicate that "primary prevention" is only a conventional definition and that the transition from primary to secondary prevention represents a continuum of increasing levels of CV risk. Although there are no direct proofs of a different efficacy of aspirin at different CV risk levels, in low-risk populations aspirin will appear to be less efficient. In fact, the lower number of events occurring in patients at low risk yields lower absolute numbers of events prevented. As many as 6 meta-analyses of trials of primary CV prevention with aspirin versus placebo, performed between 2009 and 2016, confirmed the above concepts and showed a concordant, significant reduction in nonfatal myocardial infarction, with no significant effects on stroke, as well as on CV and all-cause mortality. The recent demonstration of a moderate protective effect of aspirin on cancer (especially colorectal) confers, however, additional value to the use of aspirin, although unusually long durations of treatment and optimal daily compliance seem to be necessary. Because aspirin increases the bleeding risk, the evaluation of its net clinical benefit is an important point of debate. Thus, it is justified to search for a cutoff level of global CV risk above which the net clinical benefit of aspirin becomes evident. Such a threshold value has been calculated considering the data of 9 primary prevention trials, by the Thrombosis Group of the European Society of Cardiology, and has been indicated as a risk value of 2 or more major CV events per 100 persons per year. Also, in the recent 2016 US Guidelines, the main criterion adopted for the indication of aspirin is the level of global CV risk (suggested cutoff is 1 or more major CV events per 100 persons per year). Beyond the different values selected, it is seems very important to introduce to clinical practice and future trials a new criterion based on the level of global CV risk.

KEYWORDS: Primary prevention, cardiovascular risk, aspirin

RECEIVED: November 22, 2016. **ACCEPTED:** February 2, 2017.

PEER REVIEW: Five peer reviewers contributed to the peer review report. Reviewers' reports totaled 540 words, excluding any confidential comments to the academic editor.

TYPE: Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Sergio Coccheri, Via Ugo Bassi 13, I 40121, Bologna Italy.
Email: coccheris.angio@libero.it

Primary Cardiovascular Prevention: A Conventional Definition

Primary cardiovascular (CV) prevention can be defined as the pharmacological and/or nonpharmacological prophylaxis of atherothrombosis, evaluated as prevention of major cardiovascular events (MCEs) in subjects without history or clinical signs of underlying disease. Trials of CV primary prevention therefore recruit subjects who are exempt from a past or recent myocardial infarction (MI), stroke (major and minor), or symptomatic coronary artery disease (CAD) or peripheral artery disease (PAD). Main incident outcomes to be measured are MI, stroke, and cardiovascular death (CVD). Additional outcomes, such as hospitalization, revascularization for coronary disease, incident angina, all-cause mortality, and others, are sometimes added as auxiliary end points.

The above definition also indicates that the populations of these trials are composed of apparently healthy persons, not necessarily investigated for the presence or absence of risk factors, biomarkers, or features of organ or tissue damage related to CVD.

For these reasons, the concept of primary prevention is rather weak and subject to evolution and changes, and the results of trials so defined are difficult to apply. The transition from primary to secondary prevention is in fact not dichotomous but rather represents a continuum.

In some trial settings, the presence of one or more of these features can be a requirement for enrollment. This is still denominated primary prevention, performed in a population that although apparently "healthy" is characterized by hypertension, diabetes, asymptomatic PAD, or similar features.

In consequence, populations recruited in trials defined of primary prevention will present a certain degree of heterogeneity between patients and trials, as a function of the known or apparent absence or presence of factors that can influence the level of CV risk.

Primary prevention is therefore a conventional definition, and as such, it might sooner or later become outdated and possibly substituted by "prevention in subjects with specified levels or ranges of global cardiovascular risk."[1] The risk level may be, in the future, more precisely defined and personalized by adequate investigation for new risk factors and subclinical organ damage.

Levels of CV Risk

The average risk of a primary prevention population, although variable, is anyway much lower than that of populations in secondary prevention. By reviewing a great number of trials, the global CV risk levels expressed in a number of MCEs expected

per 100 persons per year can be classified as follows. Healthy subjects (any age) bear a global CV risk <2% MCEs per year. The risk increases from 2% to 4% MCE cases per year in asymptomatic subjects with risk factors, biomarkers, or subclinical organ damage. Thus, in patients enrolled in trials of primary prevention (exempt from MCE due to atherothrombosis), the global CV risk may vary from 1% to 4% cases of MCE per year. Conversely, in conditions of secondary prevention as in cases with previous acute myocardial infarction (AMI), stroke, stable CAD, or symptomatic PAD, the estimated global risk is ⩾4% cases of MCE per year. In highly unstable conditions, such as acute coronary syndrome, the global risk sharply increases to >10 and even 20% cases of MCE per year.[2] But does the level of CV risk influence the clinical response to aspirin?

In the landmark meta-analysis of 2009 by the Antithrombotic Trialists' (ATT) Collaboration,[3] it was shown that both in primary and secondary prevention, no direct correlation existed between the levels of any of the main risk factors or the levels of global CV risk, with the relative risk reduction (RR) due to low-dose aspirin. Therefore, there is no direct indication that aspirin is more effective in patients at high risk than at low risk. On the contrary, the absolute RR with aspirin is much higher in secondary than in primary prevention because of the greater number of events occurring in subjects at higher risk; thus, more events are liable to be prevented by an appropriate drug.[2]

For these reasons, aspirin is expected to be not *less effective*, but *less efficient* in patients at low risk, that is to say, in primary prevention.

Efficiency Versus Efficacy of Aspirin in Primary Prevention

In fact, in the capital meta-analysis of 2009, the absolute effect of aspirin was low in "healthy" patients at low risk—6 cases of AMI spared per 1000 persons in 10 years—whereas in subjects at moderate or high risk, the corresponding figure varied from 20 to 30 per 1000 persons in 10 years. As said, the relative RR, reflecting aspirin efficacy, did not correlate with the risk level.[3]

Between 2011 and 2016, as many as 6 additional meta-analyses of trials of aspirin in primary prevention were published. Only the most recent one, performed in preparation of the 2016 US Preventive Services Task Force (USPSTF) Guidelines, is discussed here.[4] The main result was a significant RR for nonfatal MI (RR: 0.78), whereas the reduction in nonfatal stroke was small (RR: 0.95) and not significant. Similarly, neither CV nor all-cause mortality was significantly reduced. The RR of 0.94 for total mortality reiterated identical figures found in previous meta-analyses, probably to be attributed to non-CV mortality. In elderly patients, a somewhat greater benefit of aspirin in preventing MI was found. A sex difference, suggested by some trials, could not be confirmed.

In fact, despite these repetitive efforts by many groups, our knowledge failed to increase beyond the results of the ATT study of 2009[3]: the only identifiable and consistent effect of aspirin in primary prevention is a moderate reduction in nonfatal MI, a result already well ascertained in the first trials many years ago (1988/1989).

Aspirin in High-Risk Primary Prevention

A number of studies have also been performed on asymptomatic patients bearing predefined risk factors or signs of organ/tissue damage. These studies enrolled subjects considered at higher risk than those recruited in trials not requiring such features. Conditions studied were hypertension, diabetes, asymptomatic PAD, asymptomatic PAD with diabetes, chronic renal disease, and others. None of these conditions enhanced the efficiency of aspirin on single CV end points or on CV or all-cause mortality.

For instance, regarding diabetes, a new meta-analysis of primary CV prevention trials[5] confirmed previous studies showing a moderate reduction in nonfatal MI that drove a small difference in MCE (RR = 0.90). But other individual end points, such as stroke, CV, and total mortality, were as usual not affected.

It could therefore seem that the influence of additional risk factors or subclinical CV conditions may not be sufficient to heighten the risk of asymptomatic patients to levels comparable with those occurring in secondary prevention. However, these effects could also be due to the small size of this type of trials.

Net Benefit of Aspirin in Primary Prevention

It should be reported here that according to the more recent data of the USPSTF, the risk of major digestive bleeding under low-dose aspirin in primary prevention is increased by about 60% over baseline, corresponding to 0.3 cases of such bleeding per 1000 persons per year.[6] For intracranial hemorrhage, the figure is a 27% increase, corresponding to 0.1 cases per 1000 persons per year. Thus, although in secondary prevention the benefit of low-dose aspirin in terms of MCE averted clearly outweighs the risk of severe bleeding complications, in primary prevention the benefit-risk balance should be more carefully considered.

A cumulative review published in 2013[7] directly addressed the problem by comparing the absolute numbers of events averted (benefits) with the absolute numbers of severe bleeding events incurred (harms) in trials of primary prevention with low-dose aspirin. The study yields interesting information, especially because it allows comparison of the numbers needed to treat (NNT) for averting 1 MCE with the numbers needed to harm (NNH) for inducing a major bleeding complication. For example, the NNT = 250 for deaths averted is not too far away from the NNH = 212 for a major bleeding. Obviously, a major bleeding is in general far less severe than death, and several major bleeding events can be controlled. However, the concept of net benefit deserves a more comprehensive definition. For instance, from their meta-analysis, Xie et al[8] state that aspirin in primary prevention confers "a

significant net benefit," but by reviewing their data, one finds an NNT for preventing 1 MCE of 284 versus an NNH for inducing a major bleeding of 299: too small a difference to qualify this as a clear net benefit.

It should after all be considered that the net clinical benefit is an abstraction when applied to the single healthy person; in fact, it is widely influenced not only by the end points chosen but also by patients' preferences, as well as by the ethical responsibility of the doctor who is prescribing a drug to a healthy individual at low CV risk, exposing him to a severe side effect. In an individual setting of prevention, the net benefit cannot be defined only in terms of numbers or statistical evidences. In fact, inducing severe bleeding in a healthy person at low risk of a future CV event is ethically more demanding than inducing the same bleeding in an actual patient at high CV risk.

Low-Dose Aspirin and Prevention of Cancer

The cardiologist interested in primary prevention of CV events in (apparently) healthy persons cannot anyway neglect recent knowledge about the properties of aspirin in preventing cancer.

The evidence for this protective effect originates mainly from side observations related to studies of CV prevention. In fact, in a number of previous meta-analyses and especially in a large meta-analysis of trials of primary or secondary CV prevention with low-dose aspirin, a consistent reduction in non-vascular mortality was observed,[9] later shown to be due to a lowered cancer mortality. The effect became evident after 4 or more years of follow-up. Also, cancer incidence was lower in another study,[10] with an absolute difference of 3.13 cases on 1000 persons per year.

The quoted analysis of Sutcliffe et al[7] showed that reduction in cancer mortality was maximal after ⩾7 years of follow-up, with a significant 20% lower incidence, mainly driven by a 34% mortality reduction of colorectal cancer.

Recent evidence collected for the USPSTF puts these data in a more balanced perspective.[11] The authors state in fact that a statistically valuable evidence for a reduction in cancer mortality and incidence in aspirin trials especially emerges when including trials of both primary and secondary CV prevention with any aspirin doses (from 75 to 1200 mg/day). Daily dosing and scheduled treatment duration of at least 4 years seem also to be necessary.

The mechanism(s) involved in this anticancer effect are still debated: inhibition of the COX1 and/or the COX2 pathways by aspirin seems to be involved. The search for related biomarkers is rapidly progressing and will allow to select patients at higher risk of colorectal cancer, with or without specific family history.[12]

At any rate, according to the current knowledge, we likely can expect a moderate anticancer effect in most of the usual CV primary prevention settings, as much larger than usual duration of treatment and follow-up and strict daily compliance seem to be necessary for relevant clinical effects.

Searching for a Cutoff Level of CV Risk for Primary CV Prevention

As seen before, there is a lack of direct evidence for a positive correlation between the level of global CV risk and the efficacy of aspirin. In primary prevention, the modest effects are largely due to lesser efficiency of aspirin as a result of low absolute number of events preventable, and the consequent net benefits between thrombotic events spared and hemorrhagic events induced are small.

To search for a CV risk level above which the increased absolute number of events prevented will result in a better net benefit is therefore an important goal.

To pursue this objective, a team of scientists of the Thrombosis Group of the European Society of Cardiology (ESC) and, among them, the author of this editorial measured the average CV risk of 9 representative primary prevention trials.[13] Afterward, the association of thrombotic events averted and major bleeding episodes occurring in these trials was evaluated with a linear univariate inverse regression. The results showed that an appreciable net benefit started to appear from a risk level of 2 CV events × 100 persons per year, and above. This level corresponds to what may be indicated as medium-risk to high-risk primary prevention. More details are available in the full paper.[13]

Guidelines, Recommendations, and Individualized Treatment

In this situation of uncertainty, a number of contradictory guidelines and recommendations have been issued.

The ESC recommends against the use of low-dose aspirin in persons exempt from cardiovascular or cerebrovascular events or disease, in view of the described uncertain net benefit.[14] A similar attitude was adopted by the Joint British Societies that do not recommend low-dose aspirin in asymptomatic patients even with diabetes or chronic renal disease.

In contrast, the American College of Chest Physicians (ACCP) guidelines recommend with some reservation (grade 2B) low-dose aspirin in healthy persons aged more than 50 years, independently of the presence of diabetes.[15] The American Diabetes Association (ADA) and the American Heart Association (AHA) jointly indicate the use of low-dose aspirin in asymptomatic subjects with type 2 diabetes who have a 10-year CV risk >10%, equivalent to 1 MCE per 100 persons per year.

On the basis of the described method of detection of a reasonable cutoff for CV risk, in the Working Group on Thrombosis the problem was approached keeping in mind that the transition from primary to secondary prevention consists in reality a continuum of increasing levels of CV risk.[13] On this background, we concluded first by recommending against low-dose aspirin in asymptomatic individuals with a global CV risk level less than or equal to 1 MCE per 100 persons per year. We conversely indicated the possible advantage of prescription of low-dose aspirin in patients with a risk of 2 or more MCE per

100 persons per year, provided they are not at high bleeding risk or have any history of bleeding. We finally chose to indicate the risk area between 1 and 2 as a gray zone within which aspirin could be given only in selected cases. Even in subjects at a risk equal to or above the cutoff of 2 MCE per 100 persons per year, the decision to initiate low-dose aspirin must anyway be individualized, and the choice includes the evaluation of the bleeding risk and the option to prevent colorectal cancer, if appropriate, by adequately prolonging treatment duration and follow-up.

More recently, the USPSTF[4,16] issued new guidelines recommending low-dose aspirin primary prevention of MCE and colorectal cancer to all patients aged between 50 and 59 years, bearing a CV risk higher than 1 MCE per 100 persons per year, provided their bleeding risk is low and they accept long-term treatment up to 10 years (grade B). For the decade of 60 to 69, the same criteria were proposed, but the decision becomes strictly individualized (grade C). No recommendation could be issued for persons aged less than 50 or more than 70 years.

The USPSTF position confirms our concept of a prominent value of the level of global CV risk for the indication of aspirin in healthy subjects, even if their proposed CV risk cutoff is less restrictive than ours.[17]

Conclusions

From data and discussions, reported above, it clearly emerges that the problem of primary CV prevention with low-dose aspirin is still a matter of debate. This situation of uncertainty is reflected in the contradictory positions of prestigious international bodies in their guidelines.

Some important societies, such as the ESC and the Joint British Societies, simply made a clean break recommending against low-dose aspirin in "healthy" persons. The ACCP gave prominent value to age recommending low-dose aspirin in healthy people aged more than 50 years, although with some reservation.

In turn, the position of our Thrombosis Group[13] attributes outstanding value to the level of global CV risk. Besides being accepted also by ADA and AHA for asymptomatic persons with type 2 diabetes, this concept was authoritatively adopted by the USPSTF in their 2016 guidelines, thus confirming our position independently of the different threshold proposed. The threshold levels of CV risk may in fact vary according to the mode of calculation and may be influenced by different attitudes toward drug administration to healthy persons. Regarding this, our more conservative threshold leaves ample space for nonpharmacological prevention (eg, lifestyle changes) that should anyway not be neglected at any risk level.

Finally, it seems most important to stress that the unsteady concept of primary versus secondary prevention should be substituted, in the future, by a unifying concept of prevention according to the global CV risk level. Regarding this, specific trials on populations with a predefined level or range of measured CV risk are strongly recommended.

Acknowledgements

The author is thankful to Prof. Raffaele De Caterina for his endorsement as Responsible of the Thrombosis Group of ESC. Best thanks also to Dr. Donatella Orlando for her thoughtful suggestions.

Author Contributions

The Author has been an active contributor on this topic in the Thrombosis Group of the European Society of Cardiology as documented by reference 2 and 13.

REFERENCES

1. van Venrooij FV, Stolk RP, Banga JD, Erkelens DW, Grobbee DE. Primary and secondary prevention in cardiovascular disease: an old-fashioned concept? *J Intern Med*. 2002;251:301–306.
2. De Caterina R, Orlando D, Berti V, Coccheri S. Aspirina nella prevenzione primaria delle malattie cardiovascolari: come bilanciare rischi e benefici. *G Ital Cardiol*. 2012;13:490–498.
3. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomized trials. *Lancet*. 2009;373:1849–1860.
4. Guirguis-Blake JM, Evans CV, Senger CA, O'Connor EA, Whitlock EP. Aspirin for the primary prevention of cardiovascular events: a systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164:804–813.
5. Kunutsor SK, Seidu S, Khunti K. Aspirin for primary prevention of cardiovascular and all-cause mortality events in diabetes: updated meta-analysis of randomized controlled trials. *Diabet Med*. 2017;34:316–327.
6. Whitlock EP, Burda BU, Williams SB, Guirguis-Blake JM, Evans CV. Bleeding risks with aspirin use for primary prevention in adults: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2016;164:826–835.
7. Sutcliffe P, Connock M, Gurung T, et al. Aspirin for prophylactic use in the primary prevention of cardiovascular disease and cancer: a systematic review and overview. *Health Technol Assess*. 2013;17:1–253.
8. Xie M, Shan Z, Zhang Y, et al. Aspirin for primary prevention of cardiovascular events: meta-analysis of randomized controlled trials and subgroup analysis by sex and diabetes status. *PLoS ONE*. 2014;9:e90286.
9. Mills EJ, Wu P, Alberton M, Kanters S, Lanas A, Lester R. Low-dose aspirin and cancer mortality: a meta-analysis of randomized trials. *Am J Med*. 2012;125:560–567.
10. Rothwell PM, Price JF, Fowkes FG, et al. Short-term effects of daily aspirin on cancer incidence, mortality, and non-vascular death: analysis of the time course of risks and benefits in 51 randomized controlled trials. *Lancet*. 2012;379:1602–1612.
11. Whitlock EP, Williams SB, Burba BU, et al. Aspirin Use in Adults: Cancer, All Cause Mortality, and Harms: A Systematic Evidence Review for the US Preventive Services Task Force. Rockville, MD: Agency for Health Care Research and Quality; 2015.
12. Patrignani P, Patrono C. Aspirin and cancer. *J Am Coll Cardiol*. 2016;68:967–976.
13. Halvorsen S, Andreotti F, ten Berg JM, et al. Aspirin therapy in primary cardiovascular disease prevention: a position paper of the European Society of Cardiology working group on thrombosis. *J Am Coll Cardiol*. 2014;64:319–327.
14. Piepoli MF, Hoes AW, Agnelli S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: the Sixth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice developed with the special contribution of the European Association for Cardiovascular Prevention and Rehabilitation (EACPR). *Eur Heart J*. 2016;37:2315–2381.
15. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis. 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141:e637S–e668S.
16. Siu AL; The US Preventive Services Task Force (USPSTF). Final recommendation statement. *Ann Inter Med*. 2016;164:279–296.
17. De Caterina R. Ruolo dell'aspirina a basse dosi in prevenzione primaria: una visione clinica. Giornale Italiano di Cardiologia. 2017;18(1): 1–6.