Aspirin for primary prevention in elderly hypertensive patients: to treat or not to treat?

Giovambattista Desideri and Claudio Ferri

A

spirin represents the cornerstone treatment for secondary prevention in patients with established cardiovascular disorders, in which its benefit outweighs the risk of bleeding, whereas the role of aspirin for individuals with no overt cardiovascular disease is more controversial [1,2]. Indeed, in primary prevention the relationship between benefit and harm is different, as the absolute cardiovascular event reduction is small and only slightly greater than the absolute excess in major bleedings [3]. Thus, depending on the levels of both cardiovascular and hemorrhagic risk, the relative benefit of aspirin can be counterbalanced, or even outweighed, by the risk of bleeding. For instance, a favorable balance between benefit and harm of aspirin administration in primary prevention has been described in patients with impaired renal function, in which aspirin administration has been demonstrated to be associated with a significant trend for a progressive reduction in major cardiovascular events and death, the lower the baseline glomerular filtration rate values [4], whereas studies on diabetes have so far failed to establish a favorable benefit–harm ratio [5–7]. This criticism applies mostly for elderly individuals for whom a higher risk of cardiovascular disease may increase the benefit of aspirin, but this benefit may be accompanied by an increased risk of bleeding [8–11].

In this issue of Journal of Hypertension, Ando et al. [12] furnish the findings of an analysis of data from the Japanese Primary Prevention Project (JPPP) study aiming to examine whether the overall efficacy of low-dose aspirin therapy in the primary prevention of cardiovascular events is influenced by hypertension. The JPPP study enrolled Japanese patients aged 60–85 years with hypertension, dyslipidemia, and/or diabetes, but without cardiovascular disease who had received low-dose aspirin (100 mg/day) or no aspirin and were followed during a mean follow-up period of 5.02 years. In the cohort of 12,278 hypertensive patients (mean age 70.8±6.2 years, average SBP from the baseline to the year of the events ≥140 mmHg) aspirin had no significant impact on the primary outcome of death from cardiovascular disease, nonfatal stroke, and nonfatal myocardial infarction (MI) [hazard ratio 0.95, 95% confidence interval (CI) 0.77–0.17, P = 0.61] and on the first secondary composite outcome that included the same events as the primary endpoint, and transient ischemic attack, angina pectoris, and arteriosclerotic disease requiring surgery or intervention (hazard ratio 0.88, 95% CI 0.74–1.05, P = 0.15). However, aspirin therapy was associated with decreased transient ischemic attack (hazard ratio 0.54, 95% CI 0.29–0.99, P = 0.045), ischemic events (hazard ratio 0.72, 95% CI 0.57–0.91, P = 0.0066), and cardiovascular events (hazard ratio 0.76, 95% CI 0.58–0.99, P = 0.044), with an additional trend toward decreased nonfatal MI (hazard ratio 0.58, 95% CI 0.33–1.02, P = 0.056). By contrast, serious extracranial hemorrhage was increased in patients receiving aspirin (hazard ratio 1.81, 95% CI 1.18–2.77, P = 0.0064) with an additional trend toward increased hemorrhagic stroke (hazard ratio 1.75, 95% CI 0.99–3.07, P = 0.053).

Similar findings were observed in the cohort of 2,186 normotensive elderly individuals (mean age 69.4±5.9 years) enrolled in JPPP study in which aspirin treatment did not ameliorated the primary and the first secondary composite outcome while significantly elevated the incidence of serious extracranial hemorrhage in individuals with high-normal SBP (hazard ratio 2.53, 95% CI 1.18–5.45, P = 0.0017). These results are quite relevant as there is limited evidence regarding the use of aspirin for primary prevention of cardiovascular disease in the elderly hypertensive and they should analyzed in the context of current available evidence and recommendations.

The previous European guidelines for the management of arterial hypertension suggested to consider the prescription of aspirin in hypertensive patients with reduced renal function or a high cardiovascular risk but not for hypertensive patients at low-to-moderate risk in whom absolute benefit and harm are equivalent [13,14]. Current European guidelines for hypertension did not recommend aspirin for primary prevention in hypertensive patients [15] due to the lack of evidence of a significant reduction of stroke or cardiovascular events compared with placebo in primary
Aspirin and primary prevention

prevention patients with elevated blood pressure (BP) and no previous cardiovascular disease [16]. The study by Ando et al. [12] further support this recommendation providing the evidence that the addition of low-dose aspirin to current therapies provides little benefit in the primary prevention of cardiovascular events and is associated with an increased risk of major hemorrhage, in aged Japanese hypertensive patients, particularly in those with high BP. Similar finding have been obtained by recent Japanese studies, such as the JPPP [17] and Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes, which enrolled a great amount of hypertensive patients [18,19].

More recently the Aspirin in Reducing Events in the Elderly (ASPREE) trial, which looked at 19114 men and women who were 70 years of age or older and did not have cardiovascular disease, dementia, or disability, demonstrated that the daily use of 100 mg of enteric-coated aspirin as primary prevention strategy neither prolonged disability-free survival nor resulted in a significantly lower risk of cardiovascular disease than placebo at a median follow-up of 4.7 years but was associated with a significant increase in major bleeding, which was attributed to excess intracranial and upper gastrointestinal bleeding, and a higher all-cause mortality (primarily attributed to cancer-related death) than placebo [11]. Some aspects of the ASPREE trial are noteworthy and challenge interpretation of the results due to their clinical relevance.

With regard to the composite primary outcome of death, dementia, or persistent physical disability, perhaps it was a little too pretentious to imagine that in the relatively short period of 4.7 years follow-up aspirin could have curbed pathophysiological pathways, such as those leading to disability and/or dementia, that commonly last for decades. Indeed, physical disability, that is the inability to meet the needs of daily living (bathing, dressing, toileting, transferring, walking, and feeding) is generally the consequence of a pathophysiological course that lasts years, studded with chronic diseases that progressively deplete the functional reserves of organs and systems. Disability usually represents the long-term consequence of the exposure to different risk factors or to acute or, more often, chronic comorbidities that during life course can hinder the independence and the health of elderly people [20]. Similar considerations apply to the pathogenesis of dementia which is often related to a chronic life-long exposure to various risk factors, including hypertension and diabetes [21]. Thus, the clinical manifestation of the age-related cognitive decline in the majority of cases represents the final step of a pathophysiological course that is begun many years before. Indeed, the brain has an extraordinarily large functional reserve which allows to support for many years the progressive neuronal loss and rarefaction of the network of synaptic connections that underlies cognitive decline. The onset of the first signs of cognitive decline expresses the exhaustion of this functional reserve of the brain, to the point that even the drugs commonly used for the management of dementia, such as cholinesterase inhibitors, have only a limited efficacy in slowing down the progression of dementia. In this regard, the authors of the ASPREE trial appropriately emphasize that the relatively short duration of the intervention may be important in identifying an effect of aspirin in clinical conditions, such as Alzheimer’s disease, that require a long latency between pathophysiological development and clinical appearance. Thus, the trial does not exclude a possible effect of aspirin if the administration is started at a younger age or continued for a longer period [11].

With regard to cardiovascular outcome, it is worth mentioning that this trial enrolled healthy older persons from the general population who were not selected on the basis of elevated cardiovascular risk [22]. As a consequence, the large majority of participants were at low cardiovascular risk (about two thirds of patients had ≤2 cardiovascular risk factors). None of the current guidelines recommend the use of aspirin for these individuals. According to this, only a third of patients assumed statins at the time of enrollment while the prevalence of previous regular aspirin use in the study was only 11%.

The last consideration regards the mortality outcome that has been worsened by aspirin intake in the ASPREE study mainly because of an increase in mortality due to gastrointestinal cancer [23]. This finding is quite surprising in the light of the huge number of epidemiological, experimental, and intervention scientific evidence that during the last few years had led to hypothesizing a possible protective effect of aspirin against cancer, especially of the colon-rectum [24–26]. The authors of ASPREE trial honestly affirm that in the context of previous studies their results were unexpected and should be cautiously interpreted [23].

The possibility that aspirin use could reduce gastrointestinal cancer has been recently proposed as a potential additional advantage that should be considered in the decision making process about the use of aspirin in primary prevention. A Position Paper of the European Society of Cardiology Working Group on Thrombosis suggests that aspirin should be considered in the primary prevention of cardiovascular events in both sexes at a level of risk of major cardiovascular events (death, MI, and stroke) more than two per 100 patient-years, provided they have no clear evidence of increased risk of bleeding (gastrointestinal bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk) and taking into account family history of gastrointestinal (especially colon) cancer [27]. More recently, the US Preventive Services Task Force has put the available evidence on this topic in a more balanced perspective recommending initiating low-dose aspirin use for the primary prevention of cardiovascular disease and colorectal cancer in adults aged 50–59 years who have a 10% or greater 10-year cardiovascular risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years while the decision to initiate this aspirin-based preventive approach in adults aged 60–69 years should be an individual one [28]. These recommendations underline that the use of aspirin could be justifiable if there is an adequate degree of risk to be reduced and enough time to see the effect expected in relation to the level of risk. From a pathophysiological perspective this balanced approach is quite convincing as primary and secondary prevention are only conventional definitions because the transition from primary to secondary prevention represents a continuum, of increasing from primary
Desideri and Ferri

prevention in young totally healthy individuals, to high-risk primary prevention, and then to secondary prevention [29]. In conclusion, the somewhat liberal use of aspirin in primary prevention in elderly (either hypertensive patients or normotensive) patients is not justifiable in the light of the evidence from the study of Ando et al. [12] and the recent ASPREE trial [11,22,23]. However, it seems to be opportune to consider the baby out with the bathwater because there is likely a considerable number of patients with high 10-year cardiovascular risk (e.g., greater than 10% event rate) and correspondingly low bleeding risk where use of low-dose aspirin still is beneficial for primary prevention. Indeed, results from clinical trials represents only the basis for the clinical judgment which (hopefully) still represents the right approach for a clinical decision based on a careful evaluation of individual risk/benefits balance.

ACKNOWLEDGEMENTS

Conflicts of interest

There are no conflicts of interest.

REFERENCES