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DO THE BENEFITS OF ASPIRIN EXCEED THE RISK OF MAJOR BLEEDS IN PATIENTS TREATED FOR PRIMARY PREVENTION OF CEREBROVASCULAR AND CARDIOVASCULAR DISEASE?

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Daily aspirin use has long been heralded for its cardioprotective effects, particularly in at-risk individuals like those with diabetes mellitus. However, a significant amount of research published in the last 5 years has called into question the benefits of aspirin for primary prevention of cardiovascular disease. Risk factors for gastrointestinal bleeding with aspirin use include higher dose and longer duration of use, history of gastrointestinal ulcers or upper gastrointestinal pain, bleeding disorders, renal failure, severe liver disease, and thrombocytopenia. Other factors that increase the risk of gastrointestinal or intracranial bleeding with low-dose aspirin use include concurrent anticoagulation or nonsteroidal anti-inflammatory drug use, uncontrolled hypertension, male sex, and older age. Aspirin for primary cardiovascular disease prevention should be highly individualized, based on the benefit-risk ratio assessment for the given patient.

Key words: aspirin, bleeding, cardiovascular disease, cerebrovascular disease, primary prevention, secondary prevention

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INTRODUCTION

Acetylsalicylic acid (a combination of sodium salicylate with acetyl chloride), synthesized in an industrial environment in 1897, was introduced to the market as Aspirin® in 1899. For about 70 years, it represented the mainstay of analgesic/anti-inflammatory drug therapy. Following several fundamental discoveries on its mechanism of action as an antiplatelet drug in the 1970s, aspirin has lived a second life as an anti-thrombotic agent, becoming a fundamental component of cerebrovascular and cardiovascular prevention and treatment (1,2). Making a jump from a largely over-the-counter analgesic remedy to a life-saving prescription drug represents a success story of independent translational research. However, as with other cerebrovascular and cardiovascular prevention strategies (e.g., blood pressure- or lipid-lowering drugs), low-dose aspirin can only reduce a fraction of all major vascular events. Similar to antihypertensive drugs or statins, the absolute benefits of aspirin are linearly related to the underlying cerebrovascular and/or cardiovascular risk of patients.

Although widely regarded as safe for patient-directed, over-the-counter use, aspirin is associated with a range of harms. They vary in type and severity with dosage and duration of use, and with the underlying patient risk factors. By inhibiting cyclooxygenase-1 enzyme activity, low-dose aspirin leads to mucosal damage to the gastrointestinal (GI) tract and causes erosions, ulcers, and bleeding (3-5). Cyclooxygenase-mediated antiplatelet effects also increase trivial to serious non-GI bleeding events, including intracranial bleeding events and hemorrhagic strokes (6,7). The advisability of using aspirin for the primary prevention of cerebrovascular (CBVD) and cardiovascular disease (CVD) events depends on accurately estimating harms associated with a specific prevention regimen and the absolute and relative variability in harms for any individual or targeted subpopulation.

The aim of this annotation is to report serious bleeding-related harms from aspirin used for primary prevention of CBVD and/or CVD.

ACETYLSALICYLIC ACID IN PRIMARY CEREBROVASCULAR AND CARDIOVASCULAR PREVENTION

In primary CBVD and CVD prevention, in which the risk of developing atherothrombotic events is generally low, it is essential to estimate the individual baseline risk of such events and balance it against the risk of adverse outcomes related to therapy.

The Framingham coronary heart disease (CHD) risk score (8), European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice SCORE (Systematic Coronary Risk Evaluation) (9), and American College of Cardiology/American Heart Association (AHA/ACC) Task Force risk equations (10) are commonly used tools to assess the baseline risk of undesirable treatment outcomes.

The respondents were ranked based on the ability to develop a coronary event (composite of myocardial infarction (MI) and coronary death) in 10-year period as low (<10%), moderate (10% to 20%), or high (>20%) risk (8). The SCORE system estimates 10-year risk of a fatal atherosclerotic event, and individuals are considered at low risk with a SCORE <1%, at moderate risk with a SCORE 1% and <5%, at high risk with a SCORE 5% and <10%, and at very high risk with a SCORE ≥10% (9).

Aspirin trials for primary cerebrovascular and cardiovascular prevention

In 2009, Baigent *et al.* published a meta-analysis (11) that included the first 6 primary CBVD and CVD prevention studies with about 95,000 respondents (12-17). They found that, over a 10-year period, aspirin therapy was associated with 6 fewer MI *per* 1,000 CHD low-risk persons treated. Persons at moderate and high CHD risk treated with aspirin had a more significantly reduced risk of MI (19 and 31 MIs *per* 1,000 patients treated, respectively) (8). With respect to mortality, protective effect was found to be of similar magnitude in persons at low and at moderate to high risk of CBVD and CVD. Aspirin therapy did not seem to have an effect on CBVD occurrence, and the overall reduction of CVDs was almost balanced by the increase in bleeding events throughout the baseline risk categories.

Four additional meta-analyses were published in 2011 and 2012 (18-21). Unlike previous investigations, these included patients who, although asymptomatic, were at a higher risk because of preexisting diabetes and/or asymptomatic peripheral arterial disease (PAD). In these meta-analyses, all cause mortality (but not the mortality from CBVD and CVD) was slightly but con-

sistently reduced, which is consistent with the result of Anti-Thrombotic-Trialists meta-analysis (11). In a recent research dealing with treatment strategies for patients with peripheral artery disease, it was confirmed that there was no difference in the influence of aspirin and placebo on total, CBD and CVD mortality (22).

The Japanese Primary Prevention Project (JPPP) was designed to determine whether once-daily, low-dose, enteric-coated aspirin reduces total number of atherosclerotic events (ischemic heart disease and stroke) compared with no aspirin in a total of 14,464 Japanese patients aged ≥60 with DM, hypertension, or dyslipidemia (23). The 5-year cumulative primary outcome event (death from MI, stroke, and other CVDs) rate was not significantly different between the groups (2.77% [95%CI, 2.40%-3.20%] for aspirin *vs.* 2.96% [95% CI, 2.58%-3.40%] for no aspirin; HR, 0.94 [95% CI, 0.77-1.15]; *p*=0.54). Aspirin significantly reduced the incidence of nonfatal MI (0.30 [95%CI, 0.19- 0.47] for aspirin *vs.* 0.58 [95% CI, 0.42-0.81] for no aspirin; HR, 0.53 [95% CI, 0.31-0.91]; *p*=0.02) and transient ischemic attack (TIA) (0.26 [95%CI, 0.16-0.42] for aspirin *vs.* 0.49 [95% CI, 0.35-0.69] for no aspirin; HR, 0.57 [95% CI, 0.32-0.99]; *p*=0.04), and significantly increased the risk of extracranial hemorrhage requiring transfusion or hospitalization (0.86 [95% CI, 0.67-1.11] for aspirin *vs.* 0.51 [95% CI, 0.37-0.72] for no aspirin; HR, 1.85 [95% CI, 1.22-2.81]; *p*=0.004). Once-daily 100-mg tablet of enteric-coated aspirin did not significantly reduce the risk of composite outcome of cardiovascular death, nonfatal stroke, and nonfatal MI among Japanese patients aged ≥60 with atherosclerotic risk factors (23).

Until recently, most of the previous studies (with the exception of JPPP) (23) on the use of aspirin in primary CBVD/CVD prevention included low-CVD risk patients. Unlike previous ones, the latest randomized controlled trials (RCTs) investigated the efficacy and safety of aspirin (100 mg/daily) *versus* placebo (or no aspirin) in subjects at a higher level of estimated CBVD and/or CVD risk. The primary efficacy outcome includes vascular death, nonfatal MI, and nonfatal stroke to be weighed against major bleeding (mainly GI and intracranial). The enrolled populations range from nondiabetic subjects with ≥2 or ≥3 risk factors, to elderly patients aged ≥70, or elderly with additional risk factors, and patients with diabetes mellitus (DM). The follow-up period was 4 to 7.5 years (24-26).

Despite the ever-increasing number of aspirin efficacy studies in primary CBVD and CVD involving a large number of patients, the results are still uneven or even controversial. Of the three recently published studies, ASCEND (24) ARRIVE (25) and ASPREE (26), the latter two showed no cardiovascular benefit and modest, but statistically significant excess in bleeding risk.

In the ASCEND survey, the adults with DM but no evident CVD has been randomly assigned to receive aspirin at a dose of 100 mg daily or placebo (24). The primary efficacy outcome was the first serious vascular event (MI, stroke or TIA, or death from any vascular cause, excluding any confirmed intracranial hemorrhage). The primary safety outcome was the first major bleeding event (intracranial hemorrhage, GI bleeding, sight-threatening bleeding event in the eye, or other serious bleeding). A total of 15,480 middle-aged or older DM patients were included in the study. During a mean follow-up of 7.4 years, serious vascular events occurred in a significantly lower percentage of participants in the aspirin group (8.5%) than in the placebo group (9.6%), and the difference was statistically significant ($p=0.01$). On the contrary, major bleeding events occurred in 4.1% of participants in the aspirin group, as compared with 3.2% in the placebo group (rate ratio, 1.29; 95% CI, 1.09 to 1.52; $p=0.003$). The most common was GI bleeding. The authors of the study concluded that aspirin use prevented serious vascular events in DM patients with no evident CVD at trial entry (24). Aspirin also caused major (mostly GI) bleeding events, and therefore the absolute treatment benefits were largely counterbalanced by the bleeding hazard.

The aim of ARRIVE trial was to assess the efficacy and safety of aspirin (100 mg daily) *versus* placebo in patients with a moderate estimated risk of first cardiovascular event (25). A total of 12,546 patients were enrolled in the study. Enrolled men were aged ≥ 55 and had ≥ 2 CV risk factors, while enrolled women were aged ≥ 60 and had ≥ 3 CV risk factors. Median follow-up was 60 months. Mostly mild GI bleeding events occurred in 0.97% of patients in the aspirin group *versus* 0.46% in the placebo group (HR 2.11; 95% CI 1.36-3.28; $p=0.0007$). The overall incidence of serious adverse events was 20.19% in the aspirin group and 20.89% in the placebo group. The overall incidence of adverse events was also similar in the two treatment groups. The overall incidence of treatment-related adverse events was 16.75% and 13.54% in the aspirin and placebo group ($p<0.0001$), respectively. The incidence of composite endpoint that included MI and stroke was about 4% in both groups. There were 321 documented deaths in the intention-to-treat population, but difference in the test groups was not significant. The authors of the study concluded that the role of aspirin in primary prevention among patients at moderate risk could not be addressed (25). Nonetheless, the findings with respect to aspirin effects were consistent with those observed in the previously published low-risk primary prevention studies.

The results of the ASPREE trial were published in three separate articles (26-28). The goal of this randomized, parallel and stratified trial was to evaluate

low-dose aspirin compared with placebo in healthy elderly patients. The trial involved 19,114 participants in Australia and the United States, aged ≥ 70 (or blacks and Hispanics aged ≥ 65) and free from CVD, dementia, and disability at trial entry. There were about 11% of patients with DM. The participants were randomly assigned to receive 100 mg daily of enteric-coated aspirin or placebo. The median duration of follow-up was 4.7 years. The rate of a composite of death, dementia, or persistent physical disability was 21.5 events *per* 1,000 person-years in the aspirin group and 21.2 *per* 1,000 person-years in the placebo group (hazard ratio, 1.01; 95%CI, 0.92-1.11; $p=0.79$). There was no significant difference in the frequency of CVD (fatal CVD, MI, stroke, or hospitalization for heart failure) between aspirin treated subjects and those receiving placebo (10.7 events *per* 1,000 person-years in the aspirin group *vs.* 11.3 events *per* 1,000 person-years in the placebo group). All-cause mortality was 5.9% in the aspirin group *versus* 5.2% in the placebo group ($p<0.05$). The rate of major hemorrhage (8.6 events *per* 1,000 person-years in the aspirin group *vs.* 6.2 events *per* 1,000 person-years in the placebo group; $p<0.001$), intracranial bleeding (2.5 events *per* 1,000 person-years in the aspirin group *vs.* 1.7 events *per* 1,000 person-years in the placebo group; $p>0.05$), and upper GI bleeding (2.1 events *per* 1,000 person-years in the aspirin group *vs.* 1.1 events *per* 1,000 person-years in the placebo group; $p<0.05$) was significantly higher in aspirin treated patients (26-28). Based on these results, the authors of the research concluded that among healthy elderly patients, low-dose aspirin therapy was not beneficial. Compared with placebo, aspirin did not improve disability-free survival or reduce major adverse cardiovascular events. Aspirin was associated with a significant increase in major bleeding (attributed to excess intracranial and upper GI bleeding), and an increase in all-cause mortality.

Similar to the ARRIVE trial (25), the ASPREE trial (26-28) showed no evidence for cardiovascular benefit of aspirin (hazard ratio for cardiovascular disease with aspirin *vs.* placebo, 0.95; 95%CI, 0.83-1.08), yet the risk of major bleeding was again higher with aspirin than with placebo (hazard ratio, 1.39; 95%CI, 1.18-1.62; $p<0.001$).

Very recently, Zheng and Roddick have reported results of a meta-analysis that included 13 trials with a total of 164,225 participants without CVD (29). The median age of trial participants was 62 years, 19% had DM, and the median baseline risk of primary cardiovascular outcome was 9.2% (range, 2.6%-15.9%). The primary cardiovascular outcome was a composite of cardiovascular mortality, nonfatal MI, and nonfatal stroke. The primary bleeding outcome was any major bleeding. Aspirin use was associated with significant

reductions in the composite cardiovascular outcome compared with no aspirin (57.1 *per* 10,000 participant-years with aspirin and 61.4 *per* 10,000 participant-years with no aspirin) (HR, 0.89 [95% CI, 0.84-0.95]. Aspirin use was associated with an increased risk of major bleeding events compared with no aspirin (23.1 *per* 10,000 participant-years with aspirin and 16.4 *per* 10,000 participant-years with no aspirin) (29).

Aspirin tailoring therapy

Based on large-scale observational studies, low-dose aspirin (e.g., 100 mg daily) approximately doubles the risk of major extracranial bleeds, particularly upper GI hemorrhage (30). In the meta-analysis of individual participant data from 6 primary prevention trials performed by the Antithrombotic Trialists' Collaboration, aspirin increased major GI and other extracranial bleeds by about half (0.10% *vs.* 0.07% *per* year; relative risk, 1.54; 95% CI, 1.30-1.82; $p < 0.0001$) (31), while significant bleeding was significantly less frequent in the secondary prevention trials. Interestingly, the main risk factors for coronary events, including DM, were also associated with hemorrhagic events, although for most the associations were slightly weaker for bleeding than for occlusive events (32). The benefit/risk profile of low-dose aspirin can vary substantially from an area of high risk where benefits clearly outweigh the excess of major bleeding complications to an area of low risk where the number of vascular events avoided equals the number of major bleeds caused by aspirin (33).

For primary prevention, in which risk is determined largely by age and presence or absence of DM, the benefit-risk ratio for prophylactic aspirin in current practice is exceptionally small. Thus, beyond diet maintenance, exercise, and smoking cessation, the best strategy for the use of aspirin in primary prevention of CVD may simply be to prescribe a statin instead (34). In contrast, for secondary prevention, in which risk is determined largely by the extent of atherosclerotic disease, the benefits of aspirin outweigh the risks of bleeding. Furthermore, in terms of safety, some medications (e.g., antiplatelet or anticoagulant drugs, selective serotonin reuptake inhibitors, and nonsteroidal anti-inflammatory drugs) may be considered absolute or relative contraindications to aspirin use for primary prevention because of their association with elevated bleeding risk (35-37).

CONCLUSION

Even at low or very low doses, aspirin increases the risk of bleeding events. However, absolute excess bleeding events will vary depending on individual baseli-

ne bleeding risks. Patient age is the strongest common risk factor for increased baseline bleeding, along with male gender, co-medications, and specific CBVD and/or CVD risk factors. A history of GI ulcers or bleeding greatly increases the baseline risk of bleeding. Safe treatment also implies eliminating patients using other medication that increase the risk of bleeding. For patients without safety concerns, aspirin is recommended in those with clear benefit or on a case-by-case basis by considering preferences, values, and other potential benefits when potential benefits and harms seem closely balanced. Therefore, on selecting the best candidates for prevention of CBVD and CVD, a gradual approach is required, during which candidates with the lowest risk of bleeding should be selected. Finally, aspirin may be considered for primary prevention of CBVD and CVD in both genders at a level of risk of major cardiovascular events (death, MI, and stroke) > 2 *per* 100 subject-years, provided they have no clear evidence of increased risk of bleeding (GI bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk).

R E F E R E N C E S

1. Patrono C, Garcia Rodriguez LA, Landolfi R, Baigent C. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med* 2005; 353: 2373-83.
2. Patrono C. Aspirin continues to attract research and debate, 115 years after its synthesis. *Rev Esp Cardiol* 2013; 66: 251-4.
3. Dworzynski K, Pollit V, Kelsey A *et al.* Management of acute upper gastrointestinal bleeding: summary of NICE guidance. *BMJ* 2012; 344: e3412 10.1136/bmj.e3412
4. Iwamoto J, Saito Y, Honda A, Matsuzaki Y. Clinical features of gastroduodenal injury associated with long-term low-dose aspirin therapy. *World J Gastroenterol* 2013; 19: 1673-82.
5. 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: 826-35.
6. Seshasai SR, Wijesuriya S, Sivakumaran R *et al.* Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012; 172: 209-16.
7. Behrouz R, Miller CM. Aspirin and intracerebral hemorrhage. Where are we now? *Neurol Clin Pract* 2015; 5: 11-6.
8. Vandvik PO, Lincoff AM, Gore JM *et al.* Primary and secondary prevention of cardiovascular disease: antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141: e637S-68S.

9. Perk J, De Backer G, Gohlke H *et al.* European guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2012; 33: 1635-701.
10. Goff DC Jr, Lloyd-Jones DM, Bennett G *et al.* 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014; 63: 2935-59.
11. Baigent C, Blackwell L, Collins R *et al.* Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849-60.
12. Peto R, Gray R, Collins R *et al.* Randomised trial of prophylactic daily aspirin in British male doctors. *Br Med J* 1988; 296: 313-6.
13. Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing Physicians' Health Study. *N Engl J Med* 1989; 321: 129-35.
14. Hansson L, Zanchetti A, Carruthers SG *et al.* Effects of intensive blood pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; 351: 1755-62.
15. The Medical Research Council's General Practice Research Framework. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. *Lancet* 1998; 351: 233-41.
16. Primary Prevention Project Investigators. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. *Lancet* 2001; 357: 89-95.
17. Ridker PM, Cook NR, Lee IM *et al.* A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005; 352: 1293-304.
18. Bartolucci AA, Tendera M, Howard G. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. *Am J Cardiol* 2011; 107: 1796-801.
19. Berger JS, Lala A, Krantz MJ *et al.* Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. *Am Heart J* 2011; 162: 115-24, e2.
20. Raju N, Sobieraj-Teague M, Hirsh J *et al.* Effect of aspirin on mortality in the primary prevention of cardiovascular disease. *Am J Med* 2011; 124: 621-9.
21. Seshasai SR, Wijesuriya S, Sivakumaran R *et al.* Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. *Arch Intern Med* 2012; 172: 209-16.
22. Jones WS, Schmit KM, Vemulapalli S *et al.* Treatment strategies for patients with peripheral artery disease. Rockville, MD: Agency for Healthcare Research and Quality (US); 2013 May. Report No.: 13-EHC090-EF.
23. Ikeda Y, Shimada K, Teramoto T *et al.* Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors. A randomized clinical trial. *JAMA* 2014; 312: 2510-20.
24. The ASCEND Study Collaborative Group. Effects of aspirin for primary prevention in persons with diabetes mellitus. *N Engl J Med* 2018; 379: 1529-39.
25. Gaziano M, Brotons C, Coppolecchia R *et al.* Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2018; 392: 1036-46.
26. McNeil JJ, Woods RL, Nelson MR *et al.*, on behalf of the ASPREE Investigator Group. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med* 2018; 379: 1499-508.
27. McNeil JJ, Nelson MR, Woods RL *et al.*, on behalf of the ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 2018; 379: 1519-28.
28. McNeil JJ, Wolfe R, Woods RL *et al.*, on behalf of the ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018; 379: 1509-18.
29. Zheng SL, Roddick AJ. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. *JAMA* 2019; 322: 277-87.
30. Garcia Rodriguez LA, Lin KJ, Hernandez-Diaz S, Johansson S. Risk of upper gastrointestinal bleeding with low-dose acetylsalicylic acid alone and in combination with clopidogrel and other medications. *Circulation* 2011; 123: 1108-15.
31. Antithrombotic Trialists' (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009; 373: 1849-60.
32. Antiplatelet Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients. *BMJ* 2002; 324: 71-86.
33. 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: 319-27.
34. Ridker PM. Should aspirin be used for primary prevention in the post-statin era? *N Engl J Med* 2018; 379: 1572-4.
35. Nalamachu S, Pergolizzi JV, Raffa RB, Lakkireddy DR, Taylor R Jr. Drug-drug interaction between NSAIDs and low-dose aspirin: a focus on cardiovascular and GI toxicity. *Expert Opin Drug Saf* 2014; 13: 903-17.
36. Moore N, Charles Pollack C, Butkerait P. Adverse drug reactions and drug-drug interactions with over-the-counter NSAIDs. *Ther Clin Risk Manag* 2015; 11: 1061-75.
37. Delaney JA, Opatrny L, Brophy JM, Suissa S. Drug-drug interactions between antithrombotic medications and the risk of gastrointestinal bleeding. *CMAJ* 2007; 177: 347-51.

SAŽETAK

JE LI DOBROBIT OD LIJEČENJA ASPIRINOM U BOLESNIKA KOJI GA UZIMAJU ZBOG PRIMARNE PREVECIJE MOŽDANO- I SRČANOKRVOŽILNIH BOLESTI VEĆA OD RIZIKA KRVARENJA?

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Dnevna upotreba aspirina već je dugo poznata zbog svojih zaštitnih moždano- i srčanokrvožilnih učinaka, što je osobito izraženo u osoba s visokim rizikom (npr. osoba sa šećernom bolesti). Međutim, značajan broj istraživanja objavljenih u posljednjih pet godina dovodi u pitanje prednosti aspirina u primarnoj prevenciji moždano- i srčanokrvožilnih bolesti. Čimbenici rizika za krvarenje iz probavnog sustava uzrokovanog aspirinom uključuju veću dozu i dugotrajno uzimanje lijeka, anamnezu o ulkusnoj bolesti, bolnost u žličici, poremećaje zgrušavanja krvi, zatajenje bubrega, tešku bolest jetre i trombocitopeniju. Drugi čimbenici koji povećavaju rizik od krvarenja iz probavnog sustava ili moždano krvarenje u osoba koje uzimaju nisku dozu aspirina uključuju istodobnu uporabu antikoagulacijskih lijekova ili nesteroidnih protuupalnih lijekova, nekontroliranu hipertenziju, muški spol i stariju dob. Primarna prevencija moždano- i srčanokrvožilnih bolesti uzrokovanih aspirinom mora biti prilagođena svakom pojedinom bolesniku pri čemu treba uzeti u obzir omjer koristi i štete od uzimanja lijeka.

Ključne riječi: aspirin, moždano-krvožilna bolest, srčano-krvožilna bolest, primarna prevencija, sekundarna prevencija