

UPDATE OF ANTIPLATELET THERAPY IN PATIENTS WITHOUT KNOWN CARDIOVASCULAR DISEASE

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ANTITROMBOCITNA TERAPIJA KOD BOLESNIKA KOJI NEMAJU POZNATU KARDIOVASKULARNU BOLEST

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ABSTRACT

Platelet activation and aggregation play a critical role in thrombosis, a fundamental pathophysiologic event responsible for the acute clinical manifestations of atherothrombotic events such as acute coronary syndrome, myocardial infarction, ischemic stroke/transient ischemic attack and peripheral artery disease. Dual antiplatelet therapy (low-dose aspirin plus ADP-P2Y₁₂ receptor blockers) has become the cornerstone of therapy for the management of acute and chronic coronary artery disease and the prevention of ischemic complications associated with percutaneous coronary intervention. However, dual antiplatelet therapy in primary prevention of cardiovascular disease in patients without known cardiovascular disease did not significantly reduce the risk of cardiovascular events, such as myocardial infarction, stroke or death, but significantly increased the rate of bleeding. Furthermore, despite multiple randomized controlled trials evaluating the efficacy and safety of aspirin use in patients without known cardiovascular disease, its role in primary prevention is still unclear, especially in patients with a higher risk of cardiovascular disease (non-diabetic individuals with ≥ 2 risk factors for coronary artery disease, elderly ≥ 60 years with additional risk factors, and patients with diabetes). Currently, there are four ongoing randomized controlled trials aiming to fill the missing gap in the efficacy and safety of aspirin therapy for primary prevention in these patients. The current European and United States Guidelines agree that primary prevention of cardiovascular disease is essential, but there are some substantial differences in risk estimation and treatment strategies among patients without known cardiovascular disease. This short review is focused on these differences and practical treatment approach to these patients based on present European and United States recommendations.

Keywords: Antiplatelet, aspirin, primary prevention, cardiovascular disease, coronary artery disease.

SAŽETAK

Aktivacija i adhezija trombocita imaju glavnu ulogu u procesu tromboze koja predstavlja osnovni patofiziološki događaj odgovoran za razvoj akutnih kliničkih manifestacija aterosklerotske bolesti arterija, kao što su akutni koronarni sindrom, infarkt miokarda, ishemijski moždani udar/transitorni ishemijski atak ili periferna arterijska bolest. Dvojna antitrombotična terapija (aspirin plus blokatori trombocitnih ADP-P2Y₁₂ receptora) predstavlja kamen temeljac u lečenju bolesnika sa akutnim i hroničnim oblicima ishemijske bolesti srca, kao i u prevenciji neželjenih ishemijskih kardiovaskularnih događaja, naročito nakon elektivne ili primarne perkutane koronarne intervencije. Ipak, primena dvojne antitrombotične terapije u primarnoj prevenciji kod bolesnika koji nemaju kardiovaskularnu bolest nije značajno smanjila rizik od neželjenih kardiovaskularnih događaja, kao što su infarkt miokarda, šlog ili smrt, ali je značajno povećala rizik od krvarenja. Takođe, uprkos brojnim randomizovanim studijama koje su analizirale efikasnost i bezbednost primene aspirina kod bolesnika koji nemaju kardiovaskularnu bolest, njegova primena u primarnoj prevenciji još uvek nije dovoljno jasna, naročito kod bolesnika koji imaju visok rizik za pojavu neželjenih kardiovaskularnih događaja (nedijabetičari sa >2 faktora rizika za koronarnu bolest, starije osobe >60 godina života sa pridruženim faktorima rizika za koronarnu bolest, i pacijenti sa dijabetesom). Trenutno su u toku četiri randomizovane studije čiji je primarni cilj analiza efikasnosti i bezbednosti primene aspirina u primarnoj prevenciji kod visoko rizičnih bolesnika. Važeće evropske i američke preporuke slažu se da je kod svih individua neophodna primarna prevencija od pojave kardiovaskularnih bolesti, ali postoje određene razlike između ovih preporuka koje se odnose na procenu kardiovaskularnog rizika i terapijskog pristupa kod visoko rizičnih bolesnika koji nemaju poznatu kardiovaskularnu bolest. Ovaj pregledni članak fokusiran je na ove razlike, kao i na terapijsku strategiju u primarnoj prevenciji kod ovih bolesnika, u skladu sa važećim evropskim i američkim preporukama.

Keywords: Antitrombotična terapija, aspirin, primarna prevencija, kardiovaskularna bolest, koronarna bolest.



ABBREVIATIONS

ADP - adenosine-diphosphat;	DAPT - dual antiplatelet therapy;
ACS - acute coronary syndrome;	GI - gastrointestinal bleeding;
CAD - coronary artery disease;	MI - myocardial infarction;
CHD - coronary heart disease;	NSAIDs - non-steroid anti-inflammatory drugs;
CV - cardiovascular;	PAD - peripheral artery disease;
CVD - cardiovascular disease;	PCI - percutaneous coronary intervention;
	RCT - randomized controlled trial;



INTRODUCTION

Platelet activation and aggregation play a critical role in thrombosis, a fundamental pathophysiologic event responsible for the acute clinical manifestations of atherothrombotic events such as acute coronary syndrome (ACS), myocardial infarction (MI), ischemic stroke/transient ischemic attack and peripheral artery disease (PAD)(1). Inhibition of platelet -function by combined use of aspirin (acetylsalicylic acid, ASA) and adenosine-diphosphat (ADP)-P2Y₁₂ receptor blockers is an important strategy for preventing ischemic cardiovascular (CV) events in patients with acute and chronic coronary artery disease (CAD), including those undergoing percutaneous coronary intervention (PCI)¹. Therefore, dual antiplatelet therapy (DAPT) has become the cornerstone of therapy for the management of acute and chronic CAD and the prevention of ischemic complications associated with PCI (1-2). However, DAPT for primary prevention of cardiovascular disease (CVD) in individuals with multiple risk factors for CAD did not significantly reduce the risk of CV events, such as MI, stroke, or CV death³. Only one study has evaluated the efficacy and safety of DAPT for primary CVD prevention in individuals with multiple risk factors for CAD or in patients with documented CAD, PAD or cerebrovascular disease (3). The CHARISMA trial showed that DAPT (clopidogrel 75 mg/d in combination with low-dose aspirin 75-100 mg/d) was not significantly more effective than aspirin alone (75-100 mg/d) in reducing the rate of total CV events (MI, stroke, or CV death) among these patients (OR, 1.20 [95% CI, 0.91-1.59] for individuals with multiple risk factors for CAD; OR, 0.88 [95% CI, 0.77-0.998] for patients with documented CAD, PAD or cerebrovascular disease)³. Contrary, this study suggested that DAPT was associated with a significant increase in the rate of GUSTO-defined moderate bleeding (OR, 1.62 [1.27-2.08]), especially in patients with documented CAD, PAD or cerebrovascular disease (3).

The role of aspirin in the treatment of acute CV events as well as for secondary prevention of future CV events has been well established (4-9). Despite multiple randomized controlled trials (RCTs) evaluating the efficacy and safety of aspirin use in patients without known CVD, its role in primary prevention is still unclear (10). The minority of RCTs

evaluating the use of aspirin in primary CVD prevention included patients with a higher-risk for CVD, and failed to show a significant benefit of aspirin therapy in primary prevention (10). Currently, there are four ongoing RCTs aiming to fill the missing gap in the efficacy and safety of aspirin therapy for primary prevention in these patients (10-14).

ANTIPLATELET THERAPY IN PRIMARY PREVENTION OF CARDIOVASCULAR DISEASE

Aspirin is the only antiplatelet drug investigated for primary prevention in cardiovascular disease (CVD) (15). Aspirin is irreversible non-selective inhibitor of cyclooxygenase enzyme (COX-1 and COX-2, respectively) that is responsible for formation of prostanoids, including prostaglandins, prostacyclins and platelet thromboxane (TxA₂) (1-2). It prevents synthesis of TxA₂ from arachidonic acid and therefore TxA₂-induced platelet aggregation (2, 16). Although efficacy and safety of aspirin in the treatment of patients without known CVD have been studied in 10 RCTs, the role of aspirin for the primary CVD prevention is still unclear (2, 10, 15-16). Meta-analysis of six RCTs with more than 95,000 patients without known CVD showed that aspirin monotherapy is associated with 12% proportional reduction (odd ratio [OR], 0.88 [95% CI, 0.82-0.94]) in serious CV events (MI, stroke, or CV death), mainly due to a 23% proportional reduction in non-fatal MI (OR, 0.77 [95% CI, 0.67-0.89]), with no clear reduction in stroke (OR, 0.95 [95% CI, 0.85-1.06]), and CV mortality (OR, 0.95 [95% CI, 0.78-1.15]) (17). The efficacy of aspirin monotherapy in reduction of CV events, especially non-fatal MI, was even higher in patients at moderate (10-20%) and high (>20%) Framingham coronary heart disease (CHD) risk, without significant reduction in stroke and CV mortality regardless of the patient CHD risk (15, 18). In another meta-analysis of six RCTs comparing benefits and risks of aspirin treatment for primary CVD prevention by sex, aspirin was associated with a significant 14% reduction in CV events for men (OR, 0.86 [95% CI, 0.78-0.94]) and 12% reduction in CV events for women (OR, 0.88 [95% CI, 0.79-0.99]), respectively (10, 19). Men were shown to have a 32% reduction in MI (OR, 0.68 [95% CI, 0.54-0.86]), but without sig-



Table 1. 10-years risk for CAD and stroke in men and women, respectively, at which the number of CV events prevented is closely balanced to the number of serious bleeding events (Modified from Ann Intern Med 2009;150:396-404).

Men		Women	
Age, years	10-year CAD risk, %	Age, years	10-year stroke risk, %
45-59	≥4	55-59	≥3
60-69	≥9	60-69	≥8
70-79	≥12	70-79	≥11

CAD - coronary artery disease

nificant reduction in stroke and CV mortality (19). Women were shown to have a 17% reduction in stroke (OR, 0.83 [95% CI, 0.70-0.97]), especially ischemic stroke (OR, 0.76 [95% CI, 0.63-0.93]), but without significant reduction in CV mortality and MI (19). However, there was a significant increase in risk of major bleeding in both men and women ([OR, 1.72 [95% CI, 1.35-2.20] in men; OR, 1.68 [95% CI, 1.13-2.52] in women) (19).

The optimum dose of aspirin for preventing future CV events is still unclear (20). Although RCTs for primary CVD prevention have demonstrated benefits with various regimens (75 mg and 100 mg per day, and 100 and 325 mg every other day), it seems that 75-100 mg dose of aspirin per day is effective as higher dosages (10, 20).

Conversely, the risk of bleeding events, such as major gastrointestinal (GI) and extracranial bleedings, may increase with aspirin dose (20). Additionally, bleeding risk is higher in patients at moderate and high CHD risk, as the main risk factors for CAD are also risk factors for bleeding (15, 17, 20). Recently, U.S. Preventive Services Task Force (USPSTF) Systematic Review of RCTs, cohort studies and meta-analyses comparing aspirin with placebo or no treatment for primary CVD prevention was published²¹. Cardiovascular primary prevention studies of aspirin, used over 3.8 to 10.1 years, showed a 59% increased risk for major GI bleeding (OR 1.59 [95% CI, 1.32-1.91]) and 33% increased risk for hemorrhagic stroke (OR, 1.33 [95% CI, 1.03-1.71]), regardless of aspirin dose. The only study with significant increase in hemorrhagic stroke (OR, 1.84 [95% CI, 1.01-3.35]) was conducted in an older hypertensive patients (21-22). Meta-analysis of six primary prevention RCTs showed that the odds of hemorrhagic strokes were significantly increased in men (OR, 1.69 [CI, 1.04 to 2.73]), but not in women (OR, 1.07 [CI, 0.42 to 2.69]) (19). Furthermore, conventional risk factors for CAD, such as age, male sex, diabetes, smoking and high blood pressure were also identified as significant risk factors for major bleeding as well (21-22). The study by Hernandez et al. has determined that significant risk factors for GI bleeding were history of peptic ulcer disease or complications, and concomitant use of non-steroid anti-inflammatory drugs (NSAIDs), anticoagulants, or other antiplatelet drug (21-23).

According to previous statements, it is essential to estimate the individual baseline risk for CV events and the absolute risk for bleeding with aspirin use, and determining its net benefit (15, 17, 21-22). The most commonly used tools for assessing baseline risk for CV events are the Framingham CHD risk score preferred by USPSTF, American Heart Association (AHA), American College of Cardiology (ACC), and American College of Chest Physicians (ACCP), and the Systematic Coronary Risk Evaluation (SCORE) preferred by European Society of Cardiology (ESC). The Framingham CHD risk score predicts the 10-year risk of CV events (composite of MI and CV death), while the SCORE system estimates the 10-year risk of fatal CVD event (death from CAD, stroke or aneurysm of the abdominal aorta) (17-18, 24-25). It is estimated that the risk of total (fatal and nonfatal) CVD events is approximately 3-times higher than the risk of fatal CVD for men, and 4-times higher in women (26).

Recently, a simple risk prediction tool for upper GI complications has been proposed (27). This tool has several disadvantages, including the incorporation of approaches to modifying the bleeding risk that are not empirically proven in a patients without known CVD and insufficient external validation to confirm its readiness for clinical application (21, 28-29).

According to USPSTF guidelines for primary CVD prevention, the net benefit of aspirin use in men depends on the initial risk for CAD events and GI bleeding, while the net benefit in women depends on the initial risk for ischemic stroke events and GI bleeding (20). Based on this data, USPSTF declared that „aspirin use for the primary CVD prevention provides more benefits than harms in men or women whose risk for MI or ischemic stroke, respectively, is high enough to outweigh the risk for GI hemorrhage” (20). The USPSTF encourage both men (age 45 to 79 years) and women (age 55 to 79 years) to use aspirin when the potential benefit of a reduction in MI and ischemic stroke, respectively, outweighs the potential harm of an increase in GI hemorrhage (Table 1). Evidence on the benefits in men <45 years and in women <55 years is limited, and the potential benefit in this age group is probably low because the risk for MI in men as well as the risk for stroke in wom-



Table 2. Fundamental recommendations for aspirin use for the primary CVD prevention from the U.S. Preventive Services Task Force (USPSTF), the American College of Chest Physicians (ACCP), the American Heart Association (AHA), the European Society of Cardiology (ESC), and the American Diabetes Association (ADA)/AHA/American College of Cardiology (ACC) Guidelines.

	Recommendations for aspirin use in primary CVD prevention			
2009 USPSTF Guidelines ²⁰	Encourage men age 45 to 79 years to use aspirin when the potential benefit of a reduction in MI outweighs the potential harm of an increase in GI hemorrhage (A recommendation)	Encourage women age 55 to 79 years to use aspirin when the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in GI hemorrhage (A recommendation)	Do not encourage aspirin use for MI prevention in men younger than 45 years and for stroke prevention in women younger than 55 years (D recommendation)	There are no recommendations for aspirin use in primary CVD prevention in men and women 80 years or older (I statement)
2012 ACCP Guidelines ¹⁸	Suggest the use of low-dose aspirin (75 to 100 mg daily) for persons aged 50 years or older. (Grade 2B)			
2002 AHA Guidelines and 2011 Update ²⁴⁻²⁵	The use of low-dose aspirin (75-160mg daily) is reasonable in persons with moderate (10-20%) and high (>20%) 10-year CHD risk (Class IIa; Level of Evidence B)		Aspirin therapy can be useful in women aged 65 years or older if blood pressure is controlled and benefit for ischemic stroke and MI prevention is likely to outweigh risk of GI bleeding and hemorrhagic stroke (Class IIa; Level of Evidence B); and may be reasonable for women aged 65 years or younger for ischemic stroke prevention (Class IIb, Level of Evidence B)	
2016 ESC Guidelines ²⁶	Antiplatelet therapy is not recommended in individuals without CVD due to the increased risk of major bleeding (Class III; Level of Evidence B)		Antiplatelet therapy (e.g. with aspirin) is not recommended for individuals with DM who do not have CVD (Class III; Level of Evidence A)	
2010 ADA/AHA/ ACCF Guidelines for aspirin use in primary CVD prevention in people with diabetes ³⁹	<div>1. Low-dose (75–162 mg daily) aspirin use for primary CVD prevention is reasonable for diabetic patients without known CVD whose 10 year risk of CV events is >10%, and who are not at increased risk for bleeding (no history of previous GI bleeding or peptic ulcer disease, or concurrent use of other medications that increase bleeding risk, such as NSAIDS or warfarin). Those adults with diabetes at increased CVD risk include most men over age 50 years and women over age 60 years who have 1 or more of the following additional major risk factors: smoking, hypertension, dyslipidemia, family history of premature CVD, and albuminuria (ACCF/AHA Class IIa; Level of Evidence B) (ADA Class IIa; Level of Evidence C)</div> <div>2. Aspirin should not be recommended in diabetes patients at low risk of CV events (men under age 50 years and women under 60 years with no major additional CVD risk factors; 10-year CVD risk under 5%) because the potential adverse effects from bleeding offset the potential benefits (ACCF/AHA Class III; Level of Evidence C) (ADA Class III; Level of Evidence C)</div> <div>3. Low-dose (75–162 mg dialy) aspirin use for primary CVD prevention might be considered for diabetic patients without known CVD at intermediate CVD risk (younger patients with 1 or more risk factors, or older patients with no risk factors, or patients with 10-year CVD risk of 5–10%) (ACCF/AHA Class IIb; Level of Evidence C) (ADA Class IIb; Level of Evidence E)</div>			

CHD - coronary heart disease; CVD - cardiovascular disease; MI - myocardial infarction;
GI - gastrointestinal bleeding.

en is very low (20). The risk of MI and stroke is high in patients older than 80 years as well as the risk of GI bleeding, and thus, the net benefit of aspirin use in octogenarians is probably much better in those without concomitant risk factors for GI bleeding (20). The ACCP guidelines for primary CVD prevention have followed similar approach to the use of aspirin (18). The 2002 AHA guidelines and 2011 update to the AHA guidelines for primary prevention of CVD and stroke recommended that both men and women with a $\geq 10\%$ 10-year risk of CHD consider taking a daily low-dose aspirin (Table 1) (24-25).

Four additional RCTs that evaluated aspirin use in asymptomatic high CVD risk patients with pre-existing

diabetes, PAD, or both showed that there were no differences in the reduction of total CV events (MI, stroke, or death) with and without use of low-dose aspirin (81-100 mg daily) (30-34). Four meta-analyses of the most aforementioned RCTs have been published recently and suggested superiority of aspirin for total CV events and non-fatal MI, but without significant reduction in stroke, CV mortality and all-cause mortality (35-38). However, there was no clear evidence of benefit in aspirin use for primary CVD prevention in these patients because of increased risk of major bleeding and hemorrhagic stroke (35-38). According to meta-analysis by Berger et al., for every 1,000 individuals treated with aspirin over a 5-year



period, aspirin would prevent 2.9 total CV events and cause 2.8 major bleeds (36). Other meta-analysis by De Berardis et al., evaluated the use of aspirin in individuals with diabetes and no CVD, and demonstrated no significant reduction in the risk of major CV events (OR, 0.90 [95% CI, 0.81-1.00]), CV mortality (OR, 0.94 [0.72 to 1.23]), or all-cause mortality (OR, 0.93 [0.82 to 1.05]) (38). Based on these data, the 2016 ESC guidelines on CVD prevention did not recommend the use of aspirin in high CVD risk patients regardless of the pre-existing diabetes (Table 2) (26). Conversely, the American Diabetes Association (ADA), the AHA, and the ACC recommend the use of low-dose aspirin (75-162 mg daily) for primary CVD prevention in diabetic patients whose 10-year risk of CV events is >10% (men age >50 years and women age >60 years with at least 1 additional risk factor: smoking, hypertension, dyslipidemia, family history of premature CV events, or albuminuria) and who are not at increased risk of bleeding (no history of previous GI bleeding or peptic ulcer disease, no concurrent use of other medications that increase bleeding risk, such as NSAID or warfarin) (Table 2) (39). Currently, there are four ongoing RCTs (ASCEND, ACCEPT-D, ASPREE, ARRIVE) aiming to fill the missing gap in the efficacy and safety of low-dose aspirin therapy for primary CVD prevention in high CHD risk individuals (non-diabetic individuals with ≥ 2 or ≥ 3 risk factors for CAD, elderly ≥ 60 years with additional risk factors, and patients with diabetes) (11-14).

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