Design and rationale for the ASSOS study: Appropriateness of aspirin use in medical outpatients a multicenter and observational study

Oğuzhan Çelik#, Cem Çil#, Bülent Özlek, Eda Özlek, Volkan Doğan, Özcan Başaran, Erkan Demirci[1], Lütfü Bekar[2], Macit Kalçık[2], Osman Karaarslan[2], Mücahit Yetim[2], Tolga Doğan[2], Vahit Demir[3], Sedat Kalkan[4], Buğra Özkan[5], Şıho Hidayet[6], Gökay Taylan[7], Zafer Küçüksu[8], Yunus Çelik[9], Süleyman Çağan Efe[10], Onur Aslan[11], Murat Biteker

Department of Cardiology, Faculty of Medicine, Muğla Sıtkı Koçman University; Muğla-*Turkey*
[1]Department of Cardiology, Kayseri Training and Research Hospital; Kayseri-*Turkey*
[2]Department of Cardiology, Hitit University Erol Olçok Training and Research Hospital; Çorum-*Turkey*
[3]Department of Cardiology, Faculty of Medicine, Yozgat Bozok University; Yozgat-*Turkey*
[4]Department of Cardiology, Pendik State Hospital; İstanbul-*Turkey*
[5]Department of Cardiology, Faculty of Medicine, Mersin University; Mersin-*Turkey*
[6]Department of Cardiology, Faculty of Medicine, Malatya İnönü University; Malatya-*Turkey*
[7]Department of Cardiology, Faculty of Medicine, Trakya University; Edirne-*Turkey*
[8]Department of Cardiology, Faculty of Medicine, Erzincan University; Erzincan-*Turkey*
[9]Department of Cardiology, Kırıkkale Yüksek İhtisas Hospital; Kırıkkale-*Turkey*
[10]Department of Cardiology, Samatya Training and Research Hospital; İstanbul-*Turkey*
[11]Department of Cardiology, Tarsus State Hospital; Mersin-*Turkey*

Abstract

Objective: The aim of this study was to describe the current status of aspirin use and the demographic characteristics of patients on aspirin for primary and secondary prevention of cardiovascular diseases.
Methods: The Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study (ASSOS) trial was a multicenter, cross-sectional, and observational study conducted in Turkey. The study was planned to include 5000 patients from 14 cities in Turkey. The data were collected at one visit, and the current clinical practice regarding aspirin use was evaluated (ClinicalTrials.gov number NCT03387384).
Results: The study enrolled all consecutive patients who were admitted to the outpatient cardiology clinics from March 2018 until June 2018. Patients should be at least 18 years old, have signed written informed consent, and on aspirin (80–325 mg) therapy within the last 30 days. Cardiologists from the hospital participates in the study. Patients were divided into 2 categories according to presence or absence of atherosclerotic cardiovascular disease, namely secondary prevention group and primary prevention group, respectively. The appropriate use of aspirin in the primary and secondary prevention groups was assessed according to the European Society of Cardiology guidelines and US Preventive Services Task Force. The patients' gastrointestinal bleeding risk factors and colorectal cancer risk were evaluated.
Conclusion: The ASSOS registry will be the most comprehensive and largest study in Turkey evaluating the appropriateness of aspirin use. The results of this study help understand the potential misuse of aspirin in a real-world setting. *(Anatol J Cardiol 2018; 20: 354-62)*
Keywords: aspirin, primary prevention, outpatients, secondary prevention

Introduction

Aspirin is a well-accepted drug for the secondary prevention of atherosclerotic cardiovascular events (1). The role of aspirin in reducing cardiovascular mortality and repeat events after acute myocardial infarction was first demonstrated nearly 30 years ago (2), and since then similar results have been demonstrated by several groups when aspirin is used for the secondary prevention of cardiovascular events (3, 4). Both low- (75–100 mg/day) and high dose aspirin were found to be effective in signifi-

#The first two authors equally contributed to this study.

Address for correspondence: Dr. Oğuzhan Çelik, Muğla Sıtkı Koçman Üniversitesi Tıp Fakültesi, Kötekli Mah. Marmaris Yolu, No:48 48000/Muğla-*Türkiye*
Phone: +90 252 214 13 26 E-mail: droguzhancelik@hotmail.com
Accepted Date: 07.09.2018 **Available Online Date:** 26.11.2018

DOI:10.14744/AnatolJCardiol.2018.47587

cantly reducing serious atherosclerotic vascular events, including stroke and coronary events, in men and women in these trials and meta-analyses (5). Therefore, several major organizations and guidelines suggest the use of daily aspirin (75–162 mg) in men and women with known coronary heart disease or atherosclerotic vascular diseases (6, 7). However, aspirin use for primary cardiovascular prevention is controversial, and the modest benefits of aspirin may be eliminated by increased bleeding in patients with no overt cardiovascular diseases (Table 1) (8-13). Therefore, guidelines and position papers differ substantially in their recommendations for aspirin use in primary prevention, reflecting the uncertainty of an exact risk/benefit ratio (Table 2) (14-19). The European Society of Cardiology (ESC) guidelines do not recommend aspirin for individuals without cardiovascular or cerebrovascular disease because of the increase in the risk of bleeding (14). The 2012 guidelines from the American College of Chest Physicians suggest the use of low-dose aspirin (75–100 mg daily) for persons aged 50 years or older without symptomatic cardiovascular disease (15). The American Stroke Association and American Heart Association recommend low-dose aspirin in patients at high risk cardiovascular events (16).

The United States Preventive Services Task Force (USPSTF) concluded that for adults aged from 50 to 59 years with a 10-year cardiovascular disease risk of 10% or greater, the benefit of aspirin for cardiovascular diseases and colorectal cancer prevention moderately outweighs the risk for harm (17). For adults aged 60 to 69 years with a 10-year cardiovascular disease risk of 10% or greater, the USPSTF concluded that the benefit of aspirin for cardiovascular disease and colorectal cancer prevention outweighs the risk for harm by a small amount (17). The USPSTF found inadequate evidence for the use of aspirin for cardiovascular disease and colorectal cancer prevention in adults younger than 50 years, or older than 69 years (17). Due to these inconsistencies between treatment guidelines, there is no approved indication for primary cardiovascular prevention in most countries, and inappropriate aspirin prescription for primary prevention is a usual finding in the real-world clinical practice. World Health Organization has recognized the problem of inappropriate medicine use in developing countries, and nearly half of all medicines are prescribed inappropriately and half of prescribed medicines are taken incorrectly by patients (20).

Although the use of cardiovascular drugs in an inappropriate indication or at inappropriate doses has been described (21, 22), off-label use or misuse of aspirin has never been studied in our country. Hence, the Appropriateness of Aspirin Use in Medical Outpatients (ASSOS) study was conducted to investigate the potential misuse of aspirin and adherence to current recommendations in the real-world setting.

Methods

Study design and setting

A multicenter, observational, cross-sectional, cohort study, termed as the ASSOS study, was conducted to address the real-world practice of aspirin use in Turkey. This national registry was designed to collect all patients receiving aspirin therapy, irrespective of the indication for use. The study was performed by hospital-based cardiologists and data were collected from 30 cardiologists in all parts of Turkey. All consecutive patients admitted to the outpatient cardiology clinics who have been prescribed aspirin were included. The study did not stipulate any diagnostic or treatment procedures. The study was approved by the Institutional Review Board or Local Ethics Committee (Muğla Sıtkı Koçman University Faculty of Medicine) and registered at ClinicalTrials.gov (NCT03387384). The sample size was calculated based on the assumption that 20% of cardiology outpatients were on aspirin therapy. We assumed that 90000 patients were

Table 1. Summary of trials evaluating aspirin for primary prevention of cardiovascular events–published in 2000 or later

Trial Country	PPP (8) Italy	WHS (9) USA	POPADAD (10) Scotland	JPAD (11) Japan	AAA (12) UK	JPPP (13) Japan
Year	2001	2005	2008	2008	2010	2014
Study design	Randomized, Open label, 2×2 factorial	Randomized, Double blind, placebo controlled	Randomized, Double blind, placebo controlled	Randomized, Open label,	Randomized, Double blind, placebo controlled	Open-label, randomized, parallel-group
Number of patients	4495	39876	1276	2539	3350	14464
Aspirin dose	100 mg/day	100 mg/day	100 mg/day	81 or 100 mg/day	100 mg/day	100 mg/day
Duration of therapy	3.7 years	10.1 years	6.7 years	4.4 years	8.2 years	5 years
Any CV events	RR=0.77 (95% CI, 0.62-0.95)	RR=0.91 (95% CI, 0.80–1.03)	RR=0.98 (95% CI, 0.76–1.26)	RR=0.80 (95% CI, 0.58–1.10)	RR=1.03 (95% CI, 0.87–1.27)	RR=0.94 (95% CI, 0.77-1.15)

PPP - Primary Prevention Project; WHS - Women's Health Study; POPADAD - Prevention of Progression of Arterial Disease and Diabetes; JPAD - Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; AAA - Aspirin for Asymptomatic Atherosclerosis, JPPP - Japanese Primary Prevention Project, CV - cardiovascular

Anatol J Cardiol 2018; 20: 354-62
DOI:10.14744/AnatolJCardiol.2018.47587

Table 2. Guidelines on the use of aspirin in primary prevention

Organization (year)	Recommendation	Class (level of evidence)
ACCP (2012) (15)	Low-dose aspirin (75–100 mg/day) in patients >50 years of age over no aspirin therapy.	II (B)
ESC/EASD (2013) (18)	Antiplatelet therapy with aspirin in patients with DM at low CVD risk is not recommended.	III (A)
ESC/EASD (2013) (18)	Antiplatelet therapy for primary prevention may be considered in high risk patients with DM on an individual basis.	IIb (C)
AHA/ADA (2015) (19)	Low-dose aspirin (75–162 mg/day) is reasonable among those with a 10-year CVD risk of at least 10% and without an increased risk of bleeding.	IIa (B)
AHA/ADA (2015) (19)	Low-dose aspirin is reasonable in adults with DM at intermediate risk (10-year CVD risk, 5%–10%).	IIb (C)
ESC (2016) (14)	Aspirin is not recommended in individuals without CVD due to the increased risk of major bleeding.	III (B)
USPSTF (2016) (17)	The USPSTF guidelines recommend initiating low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 year, and are willing to take low- dose aspirin daily for at least 10 years.	B
USPSTF (2016) (17)	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 yrs of age who have a 10% or greater 10-yr CVD risk should be an individual one. Persons who 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 are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C

CRC - colorectal cancer; CVD - cardiovascular disease; DM - diabetes mellitus; USPSTF - United States Preventive Services Task Force

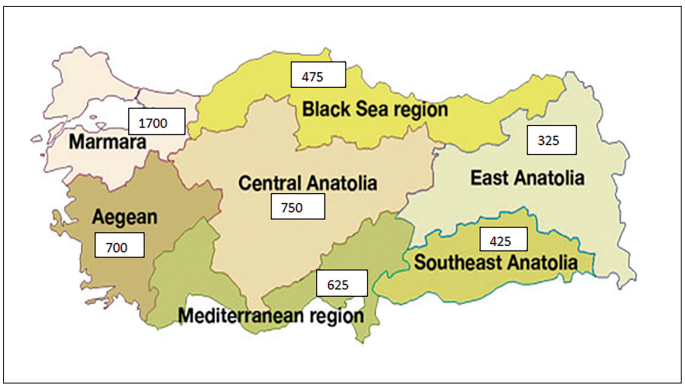

Figure 1. Geographic distribution of ASSOS study patients in Turkey by region

referred to 30 cardiologists during the 3-month period. The power calculation is based on a two-sided test, with a power of 0.90, and the margin of error was set to 1%; the required sample size was calculated as 4896. Therefore, we planned to enroll a total of 5000 patients who were on aspirin therapy in 14 cities (Muğla, İstanbul, Çorum, Yozgat, Balıkesir, Mersin, Mardin, Edirne, Kayseri, Malatya, Erzincan, Kırıkkale, İzmir, Adıyaman) from March 1, 2018, to June 31, 2018 (Fig. 1).

Patients were enrolled during a routine ambulatory visit. Turkey was divided into seven regions according to human habitat, climate, agricultural diversity, and topography during the first Geography Congress in 1941 held in Ankara. The number of patients will be proportional to the population of each region in the ASSOS study.

Inclusion criteria

- Participants aged 18 years or older at the time of enrollment,
- Patients willing to participate and provided written informed,
- Patients treated with aspirin (80–300 mg) within the last 30 days.

Exclusion criteria

- Presence of mental retardation and dissatisfaction with cooperation,
- Pregnancy.

Measurements and evaluation

Table 3 provides a summary of the items in the ASSOS survey questionnaire.

Demographic and clinical characteristics of the participants included age, gender, educational status, smoking history, place

Table 3. Variables measured in the questionnaire

Demographic information	Date of visit
	Date of birth
	Gender
	Height/weight
	Blood pressure
	Heart rate/rhythm
	Education level
	Occupation
	Smoking/alcohol
Aspirin daily dose	
Reason for aspirin use	Primary/secondary prevention
Medical specialty of the doctor who prescribed aspirin	
Medical history	Cardiovascular comorbidities
	Cardiac operations/procedures
	Concomitant diseases
	Cardiovascular risk factors
	Arrhythmias
	DM
	Chronic kidney disease
Family history	In terms of cardiovascular disease
	In terms of colerectal carsinoma
Laboratory data	Fasting blood glucose, lipid profile, urea, uric acid, creatinine, liver and thyroid function tests
History of gastrointestinal bleeding	
History of any bleeding	
HASBLED Score	Hypertension, abnormal renal/liver function, previous stroke/transient ischemic attack, bleeding history or predisposition, labile international normalized ratio, elderly (e.g., age ≥65 years, frailty), drugs/alcohol concomitantly
Concomitant drugs	

DM - diabetes mellitus; CVD - cardiovascular disease

of residence (rural or urban), body mass index, and alcohol use. Medical history, cardiovascular risk factors and all comorbidities, physical examination details, and all concomitant medications and their doses were questioned. The biochemical parameters, including fasting glucose, glycosylated hemoglobin, lipid profile, urea, uric acid, creatinine, liver, and thyroid function tests, were assessed within 3 months before the registration date. The duration of aspirin therapy, reason of use (primary or secondary prevention), and specialty of the physician who prescribed aspirin were analyzed. The complete ASSOS survey questionnaire can be found in the Supplementary Table 1. The

Supplementary Table 1. Appropriateness of aspirin use in medical outpatients: A multicenter, observational study (ASSOS Trial)

A) Demographic information

Gender
Date of visit
Date of birth
Height/weight
Occupation
Blood pressure (mm Hg)
Heart rate
Rhythm
Smoking/alcohol
Place of residence (rural or urban)
Level of education

B) Aspirin use

Aspirin daily dose
Duration (month)
Reason for aspirin use
Medical specialty of the doctor who prescribed aspirin

C) Medical history

Atrial fibrillation
Hypertension
Congestive heart failure
Diabetes Mellitus
Chronic kidney disease (GFR <60 mL/dk)
Dialyzes
Hyperlipidemia
History of myocardial infarction
Coronary artery disease
Prior CABG
Prior PCI
Peripheral artery disease (lower extremity)
Peripheral artery disease (upper extremity)
Carotid artery disease
Stroke/transient ischemic attack
Pacemaker
Bioprosthetic heart valve
Mechanical heart valve
COPD
Liver disease
Malignance

GFR - glomerular filtration rate; CABG - coronary artery bypass graft; PCI - percutaneous coronary intervention; COPD - chronic obstructive pulmonary disease

D) Gastrointestinal bleeding risk and colorectal cancer risk

Family history of colorectal cancer
Is hypertension controlled?
Did the patient have diagnosis of polyp in colon or rectum

Anatol J Cardiol 2018; 20: 354-62
DOI:10.14744/AnatolJCardiol.2018.47587

Supplementary Table 1. Cont.

D) Gastrointestinal bleeding risk and colorectal cancer risk

Did the patient use NSAİD at least 3 days a week
Did the patient have a diagnosis of ulcer
Dyspepsia
*HASBLED score
Major gastrointestinal bleeding
Intracranial bleeding
Other major bleeding
Minor bleeding

NSAID - nonsteroidal anti-inflammatory drugs; INR - international normalized ratio; ASA - acetylsalicylic acid; TTR - time in therapeutic range

***HASBLED**

H	Hypertension (>160 mm Hg)	1
A	Abnormal liver functions	1
	Abnormal renal functions	1
S	Stroke	1
B	Bleeding or anemia	1
L	Labile INR (TTR <60%)	1
E	Age >65 years	1
D	Drug (ASA/clopidogrel/NSAID)	1
	Alcohol	1

E) Drugs

Total number of drugs
ACE-I
ARB
Beta blocker
MRA
Amiodarone
Propafenone
Nondihydropiridine CCB
Dihydropyridine CCB
Digoxin
Statin
Furosemide
HCTZ
Nitrate
NSAID
Oral antidiabetic
Insulin
Warfarin
Dabigatran
Rivaroxaban
Apixaban
Edoxaban
Clopidogrel
Ticagrelor
Prasugrel
Dipyridamol

Supplementary Table 1. Cont.

E) Drugs

Ticlopidin
PPI
Steroid

ACE - angiotensin converting enzyme; ARB - angiotensin receptor blocker; MRA - mineralocorticoid receptor antagonist; CCB - calcium channel blocker; HCTZ - hydrochlorothiazide; NSAID - nonsteroidal anti-inflammatory drugs; PPI - proton pump inhibitor

F) Laboratory parameters

Fasting blood glucose
Creatinine
Sodium
Potassium
Hemoglobin
Platelet
Total cholesterol
LDL
HDL
Triglyseride

LDL - low-density lipoprotein; HDL - high-density lipoprotein

primary prevention aspirin indication was evaluated according to the 2016 ESC (14) and 2016 USPSTF guidelines (17).

There is no validated tool for bleeding risk assessment in aspirin use. The bleeding risk was determined using an existing bleeding risk stratification tool (HASBLED) and other clinical parameters. Risk factors for gastrointestinal bleeding with aspirin use, such as higher dose and longer duration of use, history of gastrointestinal bleeding, bleeding disorders, ulcers or upper gastrointestinal pain, thrombocytopenia, renal failure, severe liver disease, concurrent anticoagulation or nonsteroidal anti-inflammatory drug use, and uncontrolled hypertension were analyzed.

Risk factors for colorectal cancer, such as a history of colonic adenomatous polyps, family or personal history of colorectal cancer or familial adenomatous polyposis, alcohol intake, obesity, and smoking were also noted.

The primary endpoint of the study was the appropriate use of aspirin according to the USPSTF guidelines, and the secondary endpoint was the appropriate use of aspirin according to ESC guidelines.

Definitions

Primary prevention is defined as preventing cardiovascular disease for persons without clinically apparent cardiovascular disease.

Secondary prevention denotes preventing the recurrence of cardiovascular disease manifested by fatal or nonfatal myocardial infarction, heart failure, angina pectoris, aortic atherosclerosis and thoracic or abdominal aortic aneurysm, peripheral ar-

tery disease manifested by intermittent claudication and critical limb ischemia, and cerebrovascular disease manifested by fatal or nonfatal stroke and transient ischemic attack.

Bleeding: Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria: fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial, intraocular, intraspinal, intra-articular or pericardial, retroperitoneal, or intramuscular with compartment syndrome; bleeding causing a drop in the hemoglobin level of 2 g/dL or more or leading to transfusion of 2 or more units of whole blood or red cells (23). Minor bleeding will be defined as non-major bleeding.

HASBLED scoring system was developed and validated to predict bleeding events in patients with atrial fibrillation taking anticoagulants, but recent evidence has revealed that the HASBLED risk stratification may have relevance in the setting of antiplatelet therapy (24). HASBLED score adds one point for hypertension, abnormal renal/liver function (one point each), stroke, bleeding history or predisposition, labile international normalized ratio (INR), age older than 65 years, and drugs/alcohol concomitantly (one point each).

Statistical analysis

Mean±standard deviation or median and interquartile range was used for continuous variables. Categorical variables were summarized as frequencies and percentages. Continuous variables were compared using univariate analysis, and the chi-square test or Fisher exact test was performed for categorical variables. The Pearson or Spearman test was used for correlation analyses. A p value <0.05 was considered statistically significant.

Discussion

The ASSOS was the first study among the Turkish patients and one of the largest in the world examining the public awareness of aspirin use in primary and secondary prevention of atherosclerotic cardiovascular events. The results of the ASSOS study provide important real-world evidence and a potentially better understanding of the burden of aspirin misuse and variability in disease management in individual units. The study also provides information regarding underuse of aspirin in patients at elevated risk and overuse in those at low risk.

Although there is sufficient evidence that aspirin is beneficial in secondary cardiovascular prevention (1, 2), the results of clinical trials and meta-analyses comparing aspirin benefit in primary prevention are not homogenous (8-13). Antithrombotic Trialists' Collaboration meta-analysis included six primary prevention trials with 95.000 patients at low risk for cardiovascular events (5). During 330.000 person-years 1.671 events occurred in the aspirin group (0.51% per year) compared with 1.883 events in the control group (0.57% per year). This represents a statistically significant risk reduction for serious vascular events with a relative risk reduction of 12% and an absolute risk reduction of 0.06% per year, but this was largely due to a reduction in the first nonfatal myocardial infarction (5). Furthermore, the overall vascular mortality did not decrease significantly, and the likelihood of bleeding, including major gastrointestinal, and extracranial bleeds was significantly increased in patients taking aspirin for primary prevention (5). In a 2012 meta-analysis, nine randomized, controlled trials evaluating the use of aspirin in the primary prevention of cardiovascular and nonvascular outcomes, including cancer, with a total of 102.621 participants were analyzed (25). A relative risk reduction of 10% in total cardiovascular events was found in this meta-analysis, which might be mostly attributed to the statistically significant decline in nonfatal myocardial infarction.

However, recent data from trials published after 2000 showed that aspirin was not effective than placebo at reducing the risk of fatal or nonfatal myocardial infarction, stroke, cardiovascular death, or all-cause mortality (25). The benefit of aspirin may not be prominent as previously thought, especially when more efficacious cardiovascular disease risk reduction modalities, such as antihypertensive drugs, statins, and smoking cessation, are considered. Patients who were on aspirin therapy had a statistically significant increased risk of total bleeding and major bleeding events, and there was also no credible evidence to support aspirin use to reduce cancer mortality (25). In 2016, a comprehensive meta-analysis of 11 trials that included individual patient level data among over 118.445 men and women who were randomly assigned to either aspirin (at doses between 50 and 500 mg per day) or placebo reported a significant 22% reduction in nonfatal myocardial infarction and a significant 6% reduction in all-cause mortality but no significant benefit on nonfatal stroke (26). Due to the significant heterogeneity of the study subjects enrolled in the trials and their inconsistent results in terms of the benefit/risk balance in primary prevention patients, there are different recommendations and inconsistencies among guidelines, which can lead to overuse and underuse of aspirin (27, 28). Previous studies have shown that aspirin therapy is both overused (27) and underused (27, 28), which could be related to patient beliefs or clinician preferences. Therefore, more research is needed in this area to optimize aspirin use in the groups most likely to benefit.

Although a patient's underlying risk profile is generally taken into consideration when aspirin is recommended for primary prevention, difficulties arise in the definition of cardiovascular risk, as many different scoring systems and other metrics have been developed and used by the societies. The US guidelines are based on the Framingham Risk Score (17), while the ESC uses the Systematic Coronary Risk Evaluation (SCORE) model for cardiovascular disease mortality (18). However, information about inappropriate aspirin use from developing and transitional countries are often lacking, where there is no routine monitoring of medicine use. Therefore, we think that studies, such as ASSOS, on prescription and handling of aspirin by physicians is a critical component of efforts to improve health care worldwide,

Anatol J Cardiol 2018; 20: 354-62
DOI:10.14744/AnatolJCardiol.2018.47587

Table 4. Ongoing randomized trials assessing the benefit of aspirin for primary prevention of CVDs

Trial Country	ASCEND UK	ARRIVE Multi-Center	ACCEPT-D Italy	ASPREE Australia
Year	2005	2008	2007	2013
Study design	Randomized 2×2 factorial design, placebo controlled	Randomized, double blind, placebo controlled	Randomized, open label,	Randomized, double blind, placebo controlled
Number of patients	15480	12546	5170	16703
Aspirin dose	100 mg/day	100 mg/day	100 mg/day	100 mg/day
Duration of terapy	7.5 years	9 years	5 years	4.5 years
Any CV events	Awaited	Awaited	Awaited	Awaited

ACCEPT-D - aspirin and simvastatin combination for cardiovascular event prevention trial in diabetes; ARRIVE - aspirin to reduce risk of initial vascular event; ASCEND - a study of cardiovascular events in diabetes; ASPREE - aspirin in reducing events in the elderly; CVD - cardiovascular disease

especially in developing countries. Medication practices vary by geographic area within countries and among countries (29). Descriptive studies of prescription patterns are thus essential despite the known magnitude of the problem. Researchers need information about local factors to design appropriate intervention strategies, and local policymakers often need local results to convince them to act.

Emerging evidence suggests that aspirin may also be effective in the prevention of colorectal cancer (30). Potential benefits of aspirin in decreasing the incidence of colorectal cancer and mortality could tip the balance between risks and benefits of aspirin therapy in the primary prevention. Similar to cardiovascular risk prediction tools, several risk prediction models have been designed to assess the individual likelihood of colorectal cancer (31).

The ASSOS study evaluated patients' risk factors for colorectal cancer, including colonoscopy and adenoma history in the last 10 years, number of relatives with colorectal cancer, leisure and physical activity time, regular use of nonsteroidal anti-inflammatory drugs, smoking, vegetable intake, and body mass index.

In this regard, the development of a composite or combined prediction model for cardiovascular and colorectal cancer risk may be possible for Turkish patients, which could allow the assessment of the global risk/benefit ratio of aspirin therapy in primary prevention.

Four randomized trials are currently ongoing to assess the benefit of aspirin for the primary prevention of cardiovascular diseases: Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE; NCT00501059); Aspirin in Reducing Events in the Elderly (ASPREE; NCT01038583); A Study of Cardiovascular Events in Diabetes (ASCEND; NCT00135226); and Aspirin and Simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes (ACCEPT-D; ISRCTN48110081; Table 4). Although these studies are expected to throw more light on primary cardiovascular prevention, the findings of ASSOS study provide important real-world evidence as well as providing a potentially better understanding of the burden of inappropriate or off-label use of aspirin in Turkey.

Study limitations

The ASSOS study is a limited cross-sectional survey that provides a snapshot of the aspirin use in Turkey. Another limitation is the coverage of the study limited to outpatient cardiology clinics. Also, there is a lack of follow-up. The HASBLED score is not a perfect score and labile INR is not an indicator of bleeding events in aspirin users.

Conclusion

Despite the availability of evidence-based guidelines for aspirin therapy in primary and secondary prevention patients, it may be overused by those at low risk for cardiovascular diseases and underused by those at high risk for cardiovascular diseases because of discrepancies between consensus documents and guidelines. Therefore, the results of the ASSOS study provides a direction for future research and guides the clinical management of these patients.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – Ö.B., E.Ö., V.Doğan; Design – C.Ç., T.D., S.Ç.E., O.A.; Supervision – M.K., V.Demir, O.K., G.T.; Fundings – None; Materials – L.B., O.K., S.K., G.T.; Data collection &/or processing – E.D., M.K., T.D., S.K.; Analysis &/or interpretation – B.Özlek, L.B., Ş.H., Z.K.; Literature search – V.Demir, B.Özkan, Ş.H., M.B.; Writing – G.T., Z.K., S.Ç.E.; Critical review – E.D., Z.K., Y.Ç., O.A.

References

1. Goli RR, Contractor MM, Nathan A, Tuteja S, Kobayashi T, Giri J. Antiplatelet Therapy for Secondary Prevention of Vascular Disease Complications. Curr Atheroscler Rep 2017; 19: 56.

2. [No authors listed]. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet 1988; 2: 349-60.
3. Berger JS, Brown DL, Becker RC. Low-dose aspirin in patients with stable cardiovascular disease: a meta-analysis. Am J Med 2008; 121: 43-9.
4. Antithrombotic Trialists' (ATT) Collaboration, Baigent C, Blackwell L, Collins R, Emberson J, Godwin J, 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.
5. Antithrombotic Trialists' Collaboration. Collaborative metaanalysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324: 71-86.
6. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 64: e139–e228.
7. Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation 2016; 134: e123-55.
8. de Gaetano G; Collaborative Group of the Primary Prevention Project. 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.
9. Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, 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.
10. Belch J, MacCuish A, Campbell I, Cobbe S, Taylor R, Prescott R, et al.; Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Edinburgh. Prevention of Progression of Arterial Disease and Diabetes Study Group; Diabetes Registry Group; Royal College of Physicians Ediburgh. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ 2008; 337: a1840.
11. Ogawa H, Nakayama M, Morimoto T, Uemura S, Kanauchi M, Doi N, et al.; Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes (JPAD) Trial Investigators. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA 2008; 300: 2134-41.
12. Fowkes FG, Price JF, Stewart MC, Butcher I, Leng GC, Pell AC, et al.; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA 2010; 303: 841-8.
13. Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, 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.
14. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al.; ESC Scientific Document Group. 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 (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37: 2315-81.
15. Vandvik PO, Lincoff AM, Gore JM, Gutterman DD, Sonnenberg FA, Alonso-Coello P, 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(2 Suppl): e637S-e668S.
16. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al.; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 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 (25 Pt B): 2935-59.
17. Bibbins-Domingo K; U.S. Preventive Services Task Force. Aspirin use for the primary prevention of cardiovascular disease and colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2016; 164: 836-45.
18. Authors/Task Force Members, Rydén L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: the Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 2013; 34: 3035-87.
19. Fox CS, Golden SH, Anderson C, Bray GA, Burke LE, de Boer IH, et al.; American Heart Association Diabetes Committee of the Council on Lifestyle and Cardiometabolic Health, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council on Cardiovascular Surgery and Anesthesia, Council on Quality of Care and Outcomes Research, and the American Diabetes Association. Update on Prevention of Cardiovascular Disease in Adults With Type 2 Diabetes Mellitus in Light of Recent Evidence: A Scientific Statement From the American Heart Association and the American Diabetes Association. Circulation 2015; 132: 691-718.
20. WHO Progress in the rational use of medicines. World Health Assembly Resolution, WHA60.16, World Health Organisation, Geneva (2007). http://apps.who.int/gb/ebwha/pdf_files/whassa_wha60-rec1/e/reso-60-en.pdf p.71.
21. Biteker M, Başaran Ö, Dogan V, Beton O, Tekinalp M, Çağrı Aykan A, et al. Real-life use of digoxin in patients with non-valvular atrial

Anatol J Cardiol 2018; 20: 354-62
DOI:10.14744/AnatolJCardiol.2018.47587

fibrillation: data from the RAMSES study. J Clin Pharm Ther 2016; 41: 711-7.
22. Başaran Ö, Dogan V, Beton O, Tekinalp M, Aykan AC, Kalaycioğlu E, et al.; Collaborators. Suboptimal use of non-vitamin K antagonist oral anticoagulants: Results from the RAMSES study. Medicine (Baltimore) 2016; 95: e4672.
23. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost 2005; 3: 692-4.
24. Shah RR, Pillai A, Omar A, Zhao J, Arora V, Kapoor D, et al. Utility of the HAS-BLED Score in Risk Stratifying Patients on Dual Antiplatelet Therapy Post 12 Months After Drug-Eluting Stent Placement. Catheter Cardiovasc Interv 2017; 89: E99-E103.
25. Seshasai SR, Wijesuriya S, Sivakumaran R, Nethercott S, Erqou S, Sattar N, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med 2012; 172: 209-16.
26. 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: 804-13.
27. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: a meta-analysis on 376,162 patients. Am J Med 2012; 125: 882-7.e1.
28. VanWormer JJ, Greenlee RT, McBride PE, Peppard PE, Malecki KC, Che J, et al. Aspirin for primary prevention of CVD: are the right people using it? J Fam Pract 2012; 61: 525-32.
29. Doğan V, Başaran Ö, Biteker M, Özpamuk Karadeniz F, Tekkesin Aİ, Çakıllı Y, et al.; and Collaborators. Analysis of geographical variations in the epidemiology and management of non-valvular atrial fibrillation: results from the RAMSES registry. Anatol J Cardiol 2017; 18: 273-80.
30. Tsoi KK, Chan FC, Hirai HW, Sung JJ. Risk of gastrointestinal bleeding and benefit from colorectal cancer reduction from long-term use of low-dose aspirin: A retrospective study of 612 509 patients. J Gastroenterol Hepatol 2018; 33: 1728-36.
31. Freedman AN, Slattery ML, Ballard-Barbash R, Willis G, Cann BJ, Pee D, et al. Colorectal cancer risk prediction tool for white men and women without known susceptibility. J Clin Oncol 2009; 27: 686-93.