

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

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## 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-

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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 ap-

proved 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**

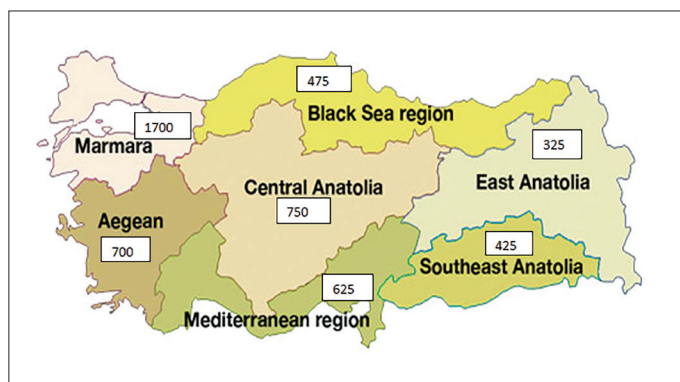
Trial Country	PPP (8) Italy	WHS (9) USA	POPADAD (10) Scotland	JPAD (11) Japan	AAA (12) UK	JPPP (13) Japan
Year	2001	2005	2008	2008	2010	2014
Study design	Randomized, Open label, 2x2 factorial	Randomized, Double blind, placebo controlled	Randomized, Double blind, placebo controlled	Randomized, Open label,	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

**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 co-operation,
- 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 colorectal carcinoma
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

Supplementary Table 1. Cont.		
<b>D) Gastrointestinal bleeding risk and colorectal cancer risk</b>		
Did the patient use NSAID 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		
<b>*HASBLED</b>		
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
<b>E) Drugs</b>		
Total number of drugs		
ACE-I		
ARB		
Beta blocker		
MRA		
Amiodarone		
Propafenone		
Nondihydropyridine 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.	
<b>E) Drugs</b>	
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	
<b>F) Laboratory parameters</b>	
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,

**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 2x2 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 therapy	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.

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