

# Appropriate Use of Aspirin in the Primary and Secondary Prevention: Results From the ASSOS Study

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## Abstract

**Objective:** Indications and appropriateness of aspirin use have not been well investigated in Turkey. Therefore, the aim of this study is to investigate the prescription patterns and appropriateness of aspirin in a real-world clinical setting. **Methods:** The ASSOS study is a cross-sectional, multicenter registry involving consecutive cardiology patients who were using aspirin. Patients were divided into two groups according to the use of aspirin; primary prevention and secondary prevention group. The indication of aspirin use was evaluated according to 2016 the European Society of Cardiology (ESC) and 2016 the United States Preventative Services Task Force (USPTF) guidelines in the primary prevention group. **Results:** A total of 5007 patients (mean age  $62.15 \pm 11.05$ , 39% female) were enrolled. The primary prevention group included 1132 (22.6%) patients and the secondary prevention group included 3875 (77.4%) patients. Of the 1132 patients, inappropriate use of aspirin was determined in 100% of the patients according to the ESC guidelines, and 71 % of the patients according to the USPTF guidelines. **Conclusion:** Although there are considerable differences between the USPTF and the ESC guidelines with respect to recommendations for aspirin use in primary prevention, inappropriate use of aspirin in Turkey is frequent in real-world practice for both guidelines.

## Introduction

Cardiovascular diseases (CVD) are responsible for nearly half of all deaths globally (1). Minimizing the impact of CVD and related disabilities is a major challenge and aspirin is the oldest and most reliable drug for this purpose (2). It is an indispensable drug in the secondary prevention of CVD (2). The net benefit is well established and supported by a large body of evidence for secondary prevention patients (3-5). However, there is no clear consensus on whom aspirin therapy is appropriate for the primary prevention of CVD.

The 2016 European Society of Cardiology (ESC) guidelines on CVD prevention did not recommend aspirin therapy in primary prevention due to increased risk of bleeding (6). While this recommendation includes both patients with and without diabetes mellitus (DM) in European guidelines, the American Diabetes Association (ADA) 2018 guidelines recommend aspirin therapy in patients with DM aged 50 years or older with at least one additional CVD risk factor, without increased risk of bleeding (7). In parallel, 2016 United States Preventative Services Task Force (USPTF) (8) and 2019 American College of Cardiology/ American Heart Association (ACC/AHA) guidelines on the primary prevention of CVD states that aspirin (75-100 mg/day) might be used in selected patients aged 40 to 70 who have high CVD risk but not increased bleeding risk (9).

Recently, three large-scale randomized controlled trials evaluated the use of aspirin in the primary prevention of CVD. These trials provided further evidence for the use of aspirin in primary prevention. The Aspirin in Reducing Events in the Elderly (ASPREE) trial enrolled elderly patients (10), the Aspirin to Reduce Risk of Initial Vascular Events (ARRIVE) trial enrolled patients with moderate to high CVD risk (11), and the A Study of Cardiovascular Events in Diabetes (ASCEND) trial enrolled patients with DM (12). While ARRIVE and ASPREE trials showed no benefit in terms of CVD risk reduction, only the ASCEND trial indicated a lower rate of major CV events, but this effect was attenuated by a higher rate of major bleeding. There was no all-cause mortality benefit in these trials (9-11). However, indications, prescription patterns, and appropriateness of aspirin use have not been well investigated with randomized or observational studies in Turkey. Therefore, the Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study (ASSOS) aims to investigate the potential misuse of aspirin in both primary and secondary prevention patients. The ASSOS is the largest multicenter domestic trial regarding this topic. The use of aspirin therapy was evaluated taking into account the risk of CVD and bleeding in this real-world trial.

## Methods

### Study design

The design of the ASSOS trial has already been described in detail (13). In brief, the ASSOS study was an observational and cross-sectional national registry study. The study was performed by 30 cardiologists in 14 different cities and the data was collected during a routine ambulatory visit from March 1, 2018, to June 31, 2018. All consecutive patients admitted to the outpatient cardiology clinics who have been prescribed aspirin, irrespective of the indication for use, were included. The study did not stipulate any diagnostic or treatment procedures. The study was approved by the Institutional Review Board of Local Ethics Committee (Muğla Sıtkı Kocman University Faculty of Medicine) and registered at ClinicalTrials.gov (NCT03387384).

The number of patients was proportional to the population of each 7 regions of Turkey. Patients aged 18 years or older at the time of enrollment, willing to participate and provided written consent, and treated with aspirin (75–100 mg) within the last 30 days were included. Pregnant patients, minors <18 years, and patients with a mental disorder were excluded.

Patients were divided into two groups according to the use of aspirin; primary prevention group patients were defined as participants who did not have any clinically apparent CVD and secondary prevention group patients were the participants who had documented CVD manifested by fatal or non-fatal myocardial infarction, angina pectoris, aortic atherosclerosis and thoracic or abdominal aortic aneurysm, peripheral artery disease manifested by intermittent claudication and critical limb ischemia, and cerebrovascular disease manifested by fatal or non-fatal stroke and transient ischemic attack.

## Data

Demographic and clinical characteristics of the participants included age, gender, educational status, smoking history, place 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 were questioned. The duration for aspirin therapy, the reason of use (primary or secondary prevention), and the specialty of the physician who prescribed aspirin were analyzed.

The indication of aspirin use was assessed according to the 2016 ESC (6) and 2016 United States Preventative Services Task Force (USPTF) guidelines (8). The risk of experiencing an atherosclerotic event was calculated using an online atherosclerotic cardiovascular disease (ASCVD) risk calculator prepared according to the 2013 ACC/AHA guidelines (14) for each individual in the primary prevention group.

The bleeding risk was determined by HASBLED and other clinical parameters. The HASBLED score adds one point for hypertension, abnormal renal/liver function (one point each), stroke, bleeding history or predisposition, labile international normalized ratio, age 65 and older, and drugs/alcohol concomitantly (one point each) (15). 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.

## Definiton of Appropriate Use of Aspirin

The appropriate use of aspirin was evaluated according to the USPTF and ESC guidelines in the primary prevention group. The ESC guidelines do not recommend aspirin for primary prevention (6). The USPTF guidelines suggest aspirin for adults age 40 to 70 at higher risk of atherosclerotic CVD without higher bleeding risk (8). Therefore, we defined aspirin use as inappropriate for all patients according to the ESC guidelines and for patients younger than 40, elder than 70, ASCVD score < 10% and, in those at high bleeding risk according to the USPTF guidelines.

## Statistical analysis

Mean  $\pm$  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 were performed for categorical variables. Multivariate logistic regression analysis was performed to find independent predictors of inappropriate aspirin use. A p-value < 0.05 was considered statistically significant. Statistical analysis was performed using statistical software (SPSS version 13.0, SPSS, Chicago, IL, USA).

## Results

A total of 5007 patients (1955 females, 39%) were enrolled and divided into primary prevention and secondary prevention groups according to the use of aspirin. The primary prevention group included 1132 (22.6%) patients and the secondary prevention group included 3875 (77.4%) patients.

## Comparison of Primary and Secondary Prevention Groups

Baseline demographic characteristics, comorbid diseases of the population demonstrated in **Table 1**. There were no significant differences between the two groups in terms of age, place of residence, the prevalence of a chronic pulmonary disease, or hepatic failure. However, patients in the secondary prevention group were more likely to be male, had a higher prevalence of DM, heart failure, hyperlipidemia, tobacco, and alcohol use. Primary prevention group patients had a higher prevalence of hypertension and atrial fibrillation compared to patients in the secondary prevention group. HASBLED scores were higher in the secondary prevention

group (**Table 1**) . While 45.9% of the patients with a HASBLED score > 2 were on proton pump inhibitor (PPI), 40.8% of HASBLED[?] 2 were on PPI (p= 0. 010).

Aspirin treatment was initiated most frequently by cardiologists (n=4167, 83.2%), followed by specialists of internal medicine (n=265, 5.3%) and neurology (n=259, 5.2%). Aspirin was used more often in secondary prevention than primary prevention by cardiologists and cardiovascular surgeons (**Fig 1** ). Other specialists prescribed aspirin mainly for primary prevention.

### Appropriate Use of Aspirin in the Primary Prevention Group

Aspirin use was inappropriate in all primary prevention patients according to ESC guidelines. Of the primary prevention patients whose ages were between 40-70 years, 324 were at high ([?]10%) ASCVD risk and low bleeding risk (HASBLED[?] 2) whereas 52 were at high ([?]10%) ASCVD risk and high bleeding (HASBLED>2) risk (**Fig 2** ). Therefore, 808 of the 1132 patients (71 %) accepted as inappropriate use of aspirin according to the USPTF guidelines. Univariate analysis showed being female, older age, smoking, educational status (illiterate), having hypertension, atrial fibrillation, heart failure, hyperlipidemia, diabetes mellitus, major bleeding history and being on OAC therapy were associated with inappropriate use of aspirin (**Table 2** ). Multivariate analysis was performed to find independent predictors of inappropriate use of aspirin in primary prevention patients. Female sex, oral anticoagulant use and heart failure were independent predictors of inappropriate aspirin use. However older age, smoking, hypertension, diabetes mellitus were associated with appropriate of aspirin use (**Table 3** ).

### Discussion

Our study showed that in a large real-world cohort of aspirin users, nearly one-fourth of the patients were receiving the drug for primary prevention. The other main findings of our study were: 1- female patients were more likely to be prescribed aspirin for primary prevention compared to males; 2- aspirin was prescribed more often for primary prevention than secondary prevention by specialists other than the cardiologists and cardiovascular surgeons; 3- the rate of inappropriate use of aspirin was high according to both ESC and USPTF guidelines in the real-world practice; 4- independent predictors of inappropriate aspirin use were female sex, oral anticoagulant use and heart failure in primary prevention patients and older age, smoking, hypertension, diabetes mellitus were associated with appropriate use of aspirin.

Although aspirin has been used in the secondary prevention of atherosclerotic events for more than 40 years (16), it has acquired a negative image in primary prevention trials which showed that aspirin did not reduce the overall mortality and did not have a net benefit (10-12).

However, there are different recommendations between the European and American guidelines regarding the use of aspirin in primary prevention. The ESC guidelines recommended that aspirin should not be used for primary prevention and subjects without clinical manifestations of CVD should not take aspirin (class III, level A) (6).

The USPTF guidelines recommended that low-dose aspirin might be considered in persons of 40 to 70 years of age who were at higher CVD risk but not at increased bleeding risk (class IIb, level A), whereas it should not be routinely administered in subjects aged >70 years (class III, level B) and should be avoided in subjects of any age at increased risk of bleeding (class III, level C) (8). The presence of such differences between the guidelines usually leads to physicians having different treatment recommendations for patients without overt CVD. However, indications and the appropriateness of aspirin use were not well studied among Turkish patients. In the awareness, efficacy, safety, and time in the therapeutic range of warfarin in the Turkish population study (WARFARIN-TR) all consecutive patients using warfarin were enrolled to evaluate the prevalence of the inappropriate combination of aspirin and warfarin therapy (17). Although performed on a very different patient population, the WARFARIN-TR study revealed that one-fifth of patients who receive warfarin were receiving aspirin inappropriately (17).

Data is very limited about patterns of inappropriate aspirin use in Turkey but studies from Europe (18) and the US (19,20) have previously documented overutilization of aspirin for primary prevention. Manes

and colleagues screened 20,599 patients in Italy and determined 400 patients were on treatment with aspirin for primary prevention (18). The authors found an overprescription of aspirin in 18% of the 400 patients. In a cross-sectional study, individuals aged 30–79 years in the Marshfield Epidemiologic Study Area were analyzed in the US (19). This study showed that 19% of the 16,922 individuals who were not clinically indicated for aspirin therapy for primary CVD were regular aspirin users (19). In the last study, 68,808 patients receiving aspirin for primary prevention were assessed in the US and inappropriate aspirin use frequency was detected in 11.6% of the study cohort (20). However, all of these studies performed before the publication of large randomized clinical trials (10-12) examining the use of aspirin in primary prevention, and all of these studies used different definitions for inappropriate aspirin use such as a 10- year risk of a CVD event <6% or a cardiovascular risk <1.0 event/100 patients/year. In our study, we used the definitions of current guidelines and found that inappropriate aspirin use frequency was 100% according to ESC and 71% according to USPTF guidelines. The current study also showed that 56% of the primary prevention group were female. (The current study is comprised of 56% female in the primary prevention group.) We also detected that aspirin was usually preferred and initiated by specialists other than cardiologists and cardiovascular surgeons in the primary prevention group.

Prevalence of aspirin use in primary prevention of cardiovascular disease was found 23.4% among adults 40 years or older in the National Health Interview Survey from the US. Of those 22.8% were using aspirin without a physician's recommendation. Of note older age, male sex, and cardiovascular risk factors (hypertension, hyperlipidemia, diabetes, and smoking) were statistically significantly associated with aspirin use in this study (21). Similarly, our study showed female sex, oral anticoagulant use and heart failure were independent predictors of inappropriate aspirin use, and older age, smoking, hypertension, diabetes mellitus were associated with appropriate use of aspirin.

The results of the ASSOS study revealed the overuse of aspirin in low-risk patients despite the recent introduction of randomized controlled trials and international guidelines, suggesting the need for improved management of patients who had no overt CVD.

### Limitations:

The present study has a cross-sectional design and the safety and efficacy outcomes could not be assessed. ASSOS study was conducted in different outpatient cardiology clinics however, participating institutions were geographically distributed across the country.

### Conclusions

To the best of our knowledge, the ASSOS study cohort represents the largest number of patients treated with aspirin in Turkey. The present study provides contemporary data on aspirin use both in primary prevention and secondary prevention group patients. The results of our study suggest that the overuse of aspirin is common because of physicians' poor compliance with the guideline recommendations in patients without documented CVD. Female patients who were on oral anticoagulants and had heart failure were at the highest risk for inappropriate use of aspirin however, older age, smoking, hypertension, diabetes mellitus were associated with appropriate use of aspirin. Thus, a greater emphasis should be given to these patients' characteristics.

### Figure Legend

**Figure 1.** Distribution of aspirin use in secondary and primary prevention according to specialists

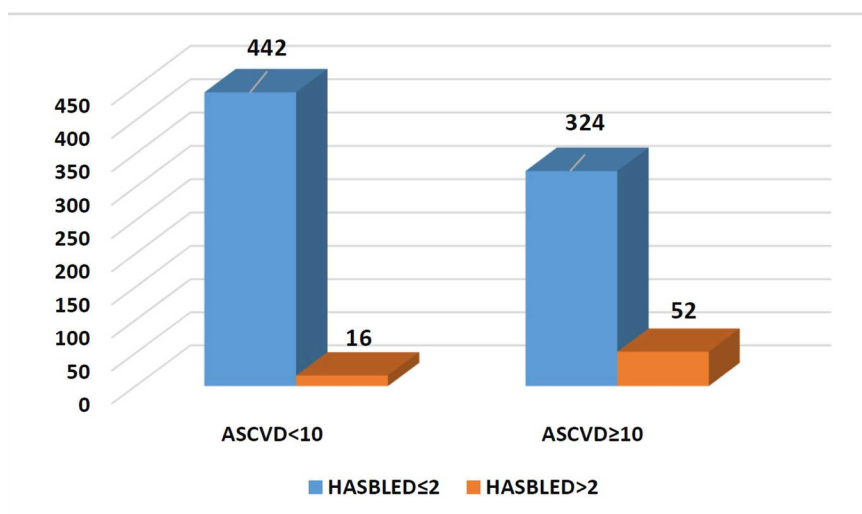
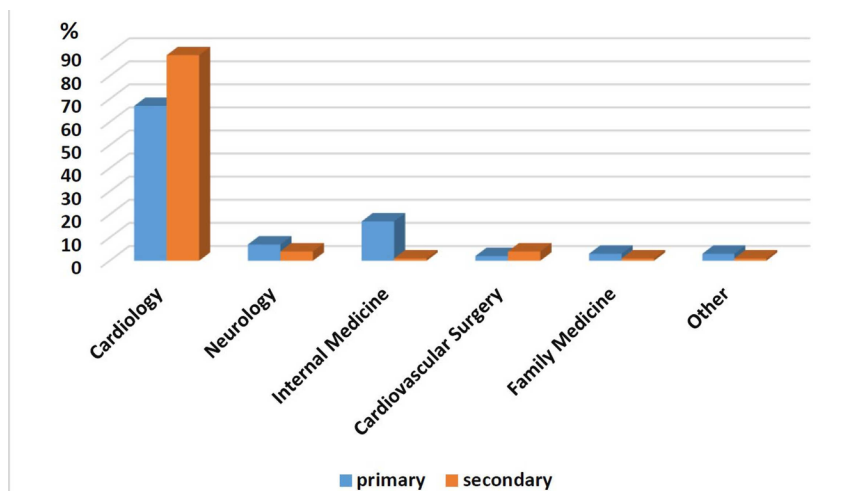
**Figure 2.** Distribution of primary prevention patients between the ages of 40-70 according to ASCVD and HASBLED score

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