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Appropriateness of aspirin use among diabetic patients in primary prevention of atherosclerotic cardiovascular diseases: an analysis of the ASSOS study

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Abstract. – OBJECTIVE: Aspirin is an essential drug in the prevention of atherosclerotic cardiovascular disease (ASCVD). It is ultimately indicated in a patient with ASCVD. However, its role is debated in primary prevention. We aimed to investigate the appropriateness of aspirin use in diabetic patients according to recommendations of recent guidelines.

PATIENTS AND METHODS: ASSOS was a multicenter observational study investigating aspirin use in cardiology outpatient clinics. We evaluated aspirin use in diabetic patients in primary prevention from the ASSOS study. We also assessed the appropriate use of aspirin according to the European Society of Cardiology (ESC), American College of Cardiology/American Heart Association (ACC/AHA), American Diabetes Association (ADA), Consensus Statement of Endocrinology, Cardiology, and Nephrology (ENCARNE), and the United States Preventive Services Task Force (USPTF).

RESULTS: A total of 5,007 patients of whom 1,537 had type 2 diabetes mellitus (DM) were included in the study. 1,132 of the total participants used aspirin for primary prevention; 313 of them had type 2 DM. Only 248 (76.7%), 132 (40.8%), and 128 (39.6%) diabetic patients indicated aspirin use according to the ESC/INCARNE, ACC/AHA, and ADA/USPTF guidelines, respectively.

CONCLUSIONS: Inappropriate aspirin use was common among diabetic patients, according to clinical practice guideline recommendations. In addition, the differences between the indications for the use of aspirin in diabetic patients according to the guidelines were remarkable. Guidelines that minimize these differences are needed for clinicians, and compliance with these guidelines in clinical practice could reduce inappropriate aspirin use.

Key Words:
Aspirin, Diabetes mellitus, Guidelines, Primary prevention, Atherosclerotic cardiovascular diseases.

Introduction

Atherosclerotic cardiovascular diseases (ASCVD), including coronary artery, cerebrovascular, and peripheral artery diseases, are responsible for approximately half of the all-cause mortality rate[1]. Diabetes mellitus (DM) is a strong risk factor for ASCVD, while the most important cause of mortality in patients with DM is ASCVD[2,3]. Many approaches aim to prevent cardiovascular diseases (CVD) and the cardiovascular effects of DM should be evaluated at the planning stage of the treatment.

Increased platelet activation due to platelet adhesion and aggression in type 2 DM causes cardiovascular events. It was hypothesized that aspirin, which acts by irreversibly blocking the

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cyclooxygenase enzyme and inhibiting thromboxane A2, could be used to prevent and treat atherosclerosis in diabetic patients[4-6]. In the early 2000s, many studies[7,8] showed that aspirin was effective for the secondary prevention of ASCVD. However, the results of large randomized controlled studies[3,9-11], particularly in the last 4 years, have shown that the limited benefit of aspirin in primary prevention is balanced by the side effect of bleeding. These results have been emphasized in current guidelines stating that aspirin should only be used for patients with a low risk of bleeding and a high risk of cardiovascular events.

The role of aspirin in the primary and secondary prevention of ASCVD was investigated in the "Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study" (ASSOS), which is the largest study to investigate the appropriateness of aspirin use in Turkey[12]. In this study, which is a sub-analysis of ASSOS, we aimed to assess the preferences regarding the clinical use of aspirin in diabetic patients in Turkey in accordance with current recommendations of recent guidelines.

Patients and Methods

Design and Context of the Study

The ASSOS is a multicenter, observational, cross-sectional cohort study. Data were collected from all patients receiving regular aspirin therapy, regardless of the indication, by cardiologists in 14 cities across Turkey between March 1 and June 30, 2018. Patients aged ≥ 18 years who took regular low-dose aspirin (80-325 mg) for any reason during the last 30 days (or more) participated in the study after providing written informed consent. Pregnant women and patients < 18 years were excluded.

The demographic characteristics, clinical diagnoses, physical examination findings, risk factors, medications, and laboratory values of the patients were examined. The reason for using aspirin, duration of use, and dose were all recorded. The HAS-BLED score was used to determine the bleeding risk[13]. Stroke, hypertension, bleeding history or tendency, impaired renal or liver function, labile international normalized ratio, medication or alcohol use, and age ≥ 65 years all contributed 1 point to the HAS-BLED score. The International Society on Thrombosis and Hemostasis defined major bleeding as fatal bleeding and/or symptomatic bleeding in a critical area or organ, such as intracranial bleeding, pericardial bleeding, bleeding causing a drop in hemoglobin of ≥ 2 g/dL, or bleeding requiring transfusion of ≥ 2 units of the whole blood[14]. Minor bleeding was simply defined as non-major bleeding. A blood glucose level > 126 mg/dL was considered to indicate DM. Individuals who were already using antidiabetic drugs were considered diabetic.

The characteristics of the diabetic patients were analyzed. Compliance with aspirin use according to the European Society of Cardiology (ESC)[15], American College of Cardiology/American Heart Association (ACC/AHA)[16], American Diabetes Association (ADA)[2], Consensus Statement of Endocrinology, Cardiology, and Nephrology (ENCARNE)[17], and the United States Preventive Services Task Force (USPTF)[18] guidelines were evaluated in patients in the primary prevention group. Those with a HAS-BLED score > 2 in the assessment of compliance according to the guidelines were considered to have a high bleeding risk. CVD risk was evaluated according to the "risk score cut-off" of the relevant guidelines.

Statistical Analysis

SPSS statistical software version 21.0 was used to conduct the analysis (IBM Corp., Armonk, NY, USA). Continuous variables are expressed as the mean and standard deviation or median and interquartile range. Frequencies and percentages were calculated for categorical variables. Continuous variables were compared using univariate analysis (Student's *t*-test or the Mann-Whitney U test), while categorical variables were compared using the chi-square or Fisher's exact test. A p-value < 0.05 was considered significant.

Results

A total of 5,007 patients, 1,537 of whom had DM, were included in the study. The majority of the diabetic patients were female (64.6%), and they were older (63.65 ± 11.29 *vs.* 61.08 ± 12.07 years) and had a higher body mass index (30.66 ± 5.36 *vs.* 28.42 ± 4.92) compared to non-diabetic patients (Table I). The DM rate was also higher in patients using aspirin for secondary protection. Diabetic patients were more likely to have

Table I. Characteristics of all patients.

	Diabetic (n = 1,537)	Non-diabetic (n = 3,470)	*p*-value
Female sex	809 (52.6)	2,243 (64.6)	< 0.001
Age, years	63.24 ± 10.25	61.67 ± 11.36	< 0.001
Body mass index	29.62 ± 4.94	28.0 ± 4.31	< 0.001
Smoking	769 (50.0)	1,999 (57.6)	< 0.001
Alcohol use	98 (6.4)	238 (6.9)	0.529
Educational status			0.021
Illiterate	258 (16.8)	532 (15.3)	
Primary	741 (48.2)	1,591 (45.9)	
Secondary	199 (12.9)	473 (13.6)	
High	234 (15.2)	655 (18.9)	
University	105 (6.8)	219 (6.3)	
Place of residence			0.433
Rural	318 (20.7)	754 (21.7)	
Urban	1,219 (79.3)	2,716 (78.3)	
Hypertension	1,203 (78.3)	2,264 (65.2)	< 0.001
Hypertension (uncontrolled)	393 (25.6)	1,206 (34.8)	< 0.001
Atrial fibrillation	81 (5.3)	241 (6.9)	0.026
Heart Failure	248 (16.1)	494 (14.2)	< 0.081
MI	603 (39.2)	1,152 (33.2)	<0.001
Chronic kidney disease	144 (9.4)	103 (3,0)	< 0.001
Dialysis	24 (1.6)	141 (4.1)	< 0.001
Hyperlipidemia	958 (62.3)	1,619 (46.7)	< 0.001
COPD	197 (12.8)	291 (8.4)	< 0.001
Malignancy	29 (1.9)	51 (1.5)	0.278
Major bleeding	34 (2.2)	64 (1.9)	0.427
Minor bleeding	236 (15.4)	398 (11.5)	< 0.001
HAS-BLED	2 (1-2)	1 (1-2)	< 0.001
Aspirin dose			0.274
≤ 100 mg	1,433 (93.2)	3,238 (93.3)	
150 mg	61 (4.0)	157 (4.5)	
300 mg	43 (2.8)	75 (2.2)	

COPD: Chronic Obstructive Pulmonary Disease; MI: myocardial infarction.

a history of hypertension ($p = 0.017$), myocardial infarction ($p < 0.001$), hyperlipidemia ($p < 0.001$), and chronic renal failure ($p < 0.001$) compared to non-diabetic patients (Table I). The minor bleeding rate ($p < 0.001$) and median HAS-BLED score [2 (range: 1-2) *vs.* 1 (1-2)] were higher in diabetic patients than in nondiabetic patients ($p < 0.001$).

In total, 1,132 of the patients included in this study were classified into the primary prevention group; 313 of these patients were diabetic. Patients with DM in the primary prevention group were older (63.65 ± 11.29 *vs.* 61.08 ± 12.07 years) and had more comorbidities comparing to non-diabetic patients (Table II). When diabetic patients in the primary prevention group were assessed according to bleeding (HAS-BLED) and CVD (SCORE®) risks, 5 patients had a low bleeding risk and low CVD risk, whereas 248 patients had low bleeding risk and high CVD risk (Figure 1). On the other hand, 60 patients had a high bleeding risk, and 25% of these patients had a low CVD risk. Also, diabetic patients were evaluated according to the ESC and ENCARNE guidelines, 41% of patients had 2 risk factors, 28% of patients had one risk factor, and 19% had 3 risk factors (Figure 2).

According to the ESC and ENCARNE guidelines, 248 (76.7%) patients with DM in primary prevention indicated aspirin. According to the ACC/AHA guidelines, aspirin was indicated in 324 (28.6%) patients, 132 (40.8%) of whom were diabetic. The use of aspirin for primary prevention of diabetic patients was inappropriate in 59.2% of cases according to the ACC/AHA guidelines. According to the ADA and USPTF guidelines, only 128 (39.6%) diabetic patients had aspirin indications in primary prevention (Figure 3).

Table II. Characteristics of patients with primary prevention.

	Diabetic (n = 313)	Non-diabetic (n = 819)	*p*-value
Female sex	202 (64.5)	432 (52.7)	< 0.001
Age, years	63.65 ± 11.29	61.08 ± 12.07	< 0.001
Body mass index	30.66 ± 5.36	28.42 ± 4.92	< 0.001
Hypertension	250 (79.9)	598 (73.0)	0.017
Hypertension (uncontrolled)	77 (24.6)	289 (35.3)	< 0.001
Atrial fibrillation	25 (8.0)	74 (9.0)	0.577
Heart Failure	32 (10.2)	67 (8.2)	0.276
Chronic kidney disease	24 (7.7)	20 (2.4)	< 0.001
Hyperlipidemia	150 (47.9)	181 (22.1)	< 0.001
COPD	43 (13.7)	66 (8.1)	< 0.001
Major bleeding	6 (1.9)	8 (1.0)	0.201
Minor bleeding	47 (15.0)	80 (9.8)	0.012
HAS-BLED	2 (1-2)	1 (1-2)	< 0.001
Aspirin dose			
≤ 100 mg	290 (92.7)	757 (92.4)	0.294
150 mg	13 (4.2)	46 (5.6)	
300 mg	10 (3.2)	16 (2.0)	

COPD: Chronic Obstructive Pulmonary Disease.

Discussion

In our study, approximately one-fourth of the patients using aspirin were diabetic, and approximately one-third of those patients were in the primary prevention group. The rate of unnecessary aspirin use was high in both diabetic and non-diabetic patients in the primary prevention group.

Aspirin has an overall significant therapeutic benefit for secondary prevention of ASCVD in adults with and without DM, on the other hand, the evidence supporting its use for primary prevention remains inconsistent[19-21]. Also, inappropriate use of aspirin for primary prevention according to the guidelines has been reported[19-22]. Although patients with DM have a higher risk of ASCVD compared to those without DM, aspirin therapy should not be started in every patient due to the bleeding tendency. In a study[22] conducted in the USA, it was reported that 26.9%

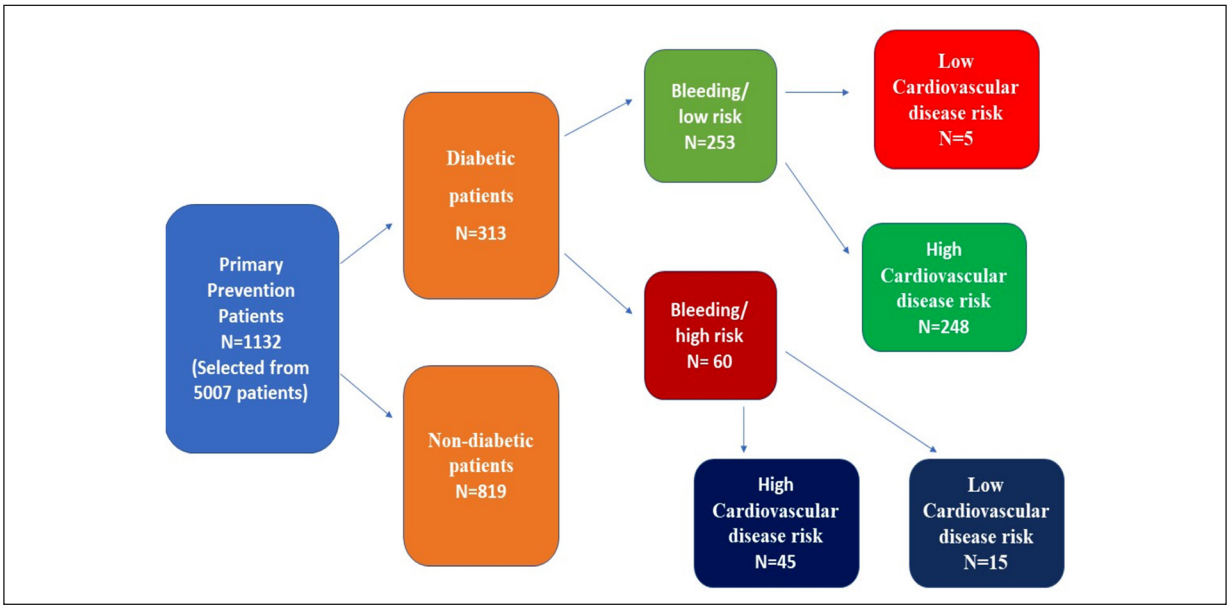

Figure 1. Distribution and characteristics of participants.

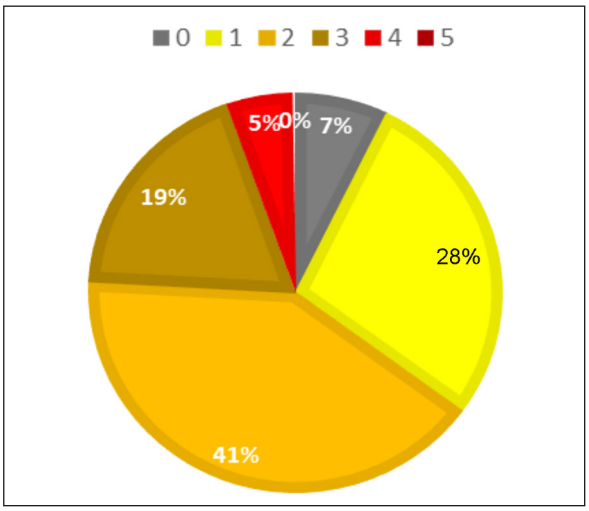

Figure 2. Coexistence rates of additional risk factors in diabetic patients according to ESC [15] and ENCARNE[17] guidelines. The patients were classified according to the coexistence rates of additional risk factors as 0-5 (from the lowest risk to the highest). Coexistence risk numbers are expressed with colors. European Society of Cardiology (ESC), Consensus Statement of Endocrinology, Cardiology, and Nephrology (ENCARNE).

of patients using aspirin had no indication for primary prevention. In another primary prevention study[23], in which most patients had DM, it

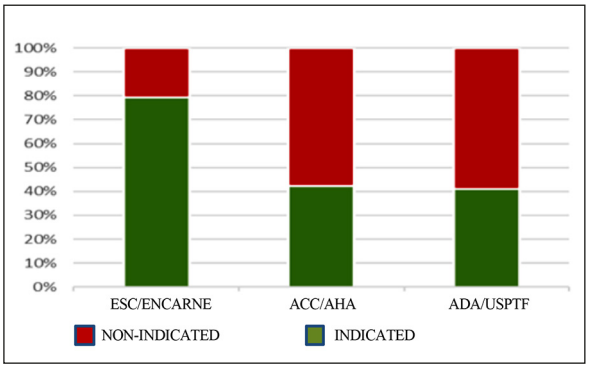

Figure 3. Appropriate use of aspirin according to ESC/ENCARNE, ACC/AHA, and ADA/USPFT guidelines[2,15-18]. European Society of Cardiology (ESC), Consensus Statement of Endocrinology, Cardiology, and Nephrology (ENCARNE), American College of Cardiology/American Heart Association (ACC/AHA), American Diabetes Association (ADA), and the United States Preventive Services Task Force (USPTF).

was found that 23% of the patients used aspirin unnecessarily. Additionally, it was shown[24] that a significant rate of patients with DM using aspirin for primary prevention had no indication according to the ACC/AHA guidelines. In our study, inappropriate aspirin use was found common among diabetic patients according to clinical practice guideline recommendations like previous studies[22-24]. The use of aspirin for primary prevention of diabetic patients was inappropriate in 59.2% of cases according to the ACC/AHA guidelines. Also, considering the ADA and USPTF guidelines, only 128 (39.6%) diabetic patients had aspirin indications in primary prevention. On the other hand, 248 (76.7%) patients with DM in primary prevention had indications of aspirin according to the ESC and ENCARNE guidelines. The differences between the indications for the use of aspirin in diabetic patients according to the guidelines were remarkable. The finding of significant differences within the same patient population when using different guidelines illustrates that there is no consensus on which patients should be given aspirin for primary prevention. Guidelines to minimize indication differences are needed for clinicians and using these indications in clinical practice could reduce inappropriate aspirin use.

Aspirin is one of the oldest antithrombotic agents that irreversibly inactivates cyclooxygenase 1. The most important factor limiting the use of aspirin for primary prevention is bleeding. On the other hand, it is known that patients who have never had ASCVD have a lower risk for future ASCVD events but assessing the benefits and risks of prophylactic aspirin for primary prevention is difficult for clinicians. According to the 2019 ACC/AHA guidelines, the risk-benefit ratio of using prophylactic aspirin generally becomes more favorable when the estimated 10-year risk of ASCVD is > 10%, and prophylactic aspirin for primary prevention in adults > 70 years of age could be harmful due to the increased risk of bleeding; thus, it is difficult to justify regular treatment with aspirin. Furthermore, there is limited data regarding the risk-benefit ratio of routine aspirin for primary prevention in patients aged < 40 years[16]. The ADA Standards of Medical Care in Diabetes (2021) and USPSTF recommend aspirin for primary prevention in adult DM patients aged ≥ 50 years who have a high CVD risk and low bleeding risk, but not in adults > 70 years of age because of the risk of bleeding[2,18]. In 2021,

the ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice recommended low-dose aspirin in DM patients with a high or very high CVD risk, for primary prevention in the absence of contraindications[15]. In addition, the ENCARNE guidelines, developed in Turkey, recommend aspirin in high-risk diabetic patients according to the ESC guidelines[17]. In our study, it was found that the use of aspirin for primary prevention in diabetic patients was inappropriate in 60.4% according to the ADA and USPSTF guidelines. Also, according to the ESC and ENCARNE guidelines, 23.3% of them used aspirin inappropriately. On this point, another factor that should be emphasized is that DM was linked to an increased risk of major bleeding episodes regardless of aspirin use (incidence rate ratio, 1.36; 95% confidence interval, 1.28-1.44)[25]. Also, it was reported that the risk of bleeding was high in a recent Danish study[26] in which aspirin was widely used for primary prevention. Although the risk of bleeding, there are no bleeding risk calculators designed specifically for diabetic patients. The major bleeding risk calculators (HAS-BLED; HEMORRHAGES, and ATRIA) do not identify DM as a risk factor for patients considering initiating antiplatelet drugs[27-29]. We used the HAS-BLED risk score, which has been validated by many studies and used for evaluating bleeding risk in clinical practice. In our diabetic patients, 5 patients had a low bleeding risk and low CVD risk, whereas 248 patients had a low bleeding risk and high CVD risk. On the other hand, 60 patients had a high bleeding risk, and 25% of these patients had a low CVD risk. Additional risk factors were more common, 41% of patients had 2 risk factors, the rate of major bleeding was higher (albeit not statistically significant), and the rate of minor bleeding was significantly higher, similar to previous studies[27-29].

Limitations

One of the main limitations is the cross-sectional design of the study. Another is that the study omitted results related to safety and efficacy. Another significant limitation of the study is that we preferred to categorize Turkey into 7 areas rather than using the Nomenclature of territorial units for statistics (NUTS) system to represent the population distribution. However, we decided to use the traditional seven areas that were established during Turkey's first geography congress based on topography, climate, agricultural diversity, and human habitat. The results do not accurately represent the entire healthcare system, including primary care and other specialties, as the study only included cardiology clinics.

Conclusions

Patients with DM have an increased risk of CVD. Aspirin is effective in reducing cardiovascular risk in patients, but the increased bleeding risk has been emphasized in recent literature, similar to our study. In our multicentre, large-scale study, unnecessary aspirin use was common among primary prevention patients. We also observed significant differences between the actual clinical use of aspirin and guidelines regarding aspirin therapy for patients with DM. Clinicians following patients with DM should be careful when prescribing aspirin for primary prevention and should consider the risk of bleeding.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Authors' Contribution

All the authors contributed to the planning, obtained data, and wrote the manuscript.

Ethics Approval

This study was approved by the Muğla Sıtkı Koçman University Clinical Research Ethics Committee [number 01/09 (01.03.2018)] and registered at ClinicalTrials.gov (NCT03387384).

Informed Consent

Informed written consent was obtained by the participants of the study.

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