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An Evaluation of Aspirin Treatment Preferences of Physicians in Hypertensive Patients in Terms of Current Guidelines: A Subgroup Analysis of the ASSOS Trial in Turkey

ORIGINAL INVESTIGATION

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ABSTRACT

Background: The Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study trial has been the largest study ever conducted among patients in Turkey regarding aspirin treatment. In the subgroup analysis of the hypertensive group of the Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study trial, we aimed to evaluate the physicians' adherence to current guidelines regarding their aspirin treatment preferences.

Methods: The Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study trial is a cross-sectional and multicenter study conducted among 5007 consecutive patients aged ≥18 years. The study population consisted of outpatients on aspirin treatment (80-300 mg). The patient data were obtained from 30 different cardiology clinics of 14 cities from all over Turkey. In this subgroup analysis, patients were divided into 2 groups: the hypertensive group (n = 3467, 69.3%) and the group without hypertension (n = 1540, 30.7%) according to the 2018 European Society of Cardiology/European Society of Hypertension Guidelines for the Management of Arterial Hypertension.

Results: Aspirin use for primary prevention was higher in patients with hypertension compared to patients without hypertension [328 (21.3%); 1046 (30.2%); $P < .001$]. Treatment with a dose of 150 mg aspirin (n = 172, 5%) was mostly preferred by internists for hypertensive patients (n =226, 6.5%); however, a daily dose of 80-100 mg aspirin therapy (n = 1457, 94.6%) was mostly prescribed by cardiologists (n = 1347, 87.5%) for patients without hypertension.

Conclusion: Aspirin was found to be used commonly among patients with hypertension for primary prevention despite the current European Society of Cardiology Arterial Hypertension Guideline not recommending aspirin for primary prevention in patients with hypertension.

Keywords: Aspirin, hypertension, primary prevention, secondary prevention, Turkey

INTRODUCTION

Hypertension (HT) is one of the most common chronic diseases and a global public health issue. Hypertension is the major risk factor in cardiovascular (CV) events and lowering blood pressure is critical in reducing morbidity and mortality due to HT.[1-3]

Low-dose aspirin use is vital to avoid negative CV effects, mainly in patients with prior CV events.[4-6] Aspirin was reported to be effective in secondary prevention (SP) of CV events in fundamental researches, clinical studies, observational epidemiologic, and randomized studies.[7] In patients without a history of CV events, aspirin reduces the risk of non-fatal myocardial infarction (MI) but increases the risk of major bleeding events. So, the balance of medical risks and benefits should be well evaluated in primary prevention (PP).[8] The use of aspirin in hypertensive patients without a known CV disease is not recommended in the 2018 European Society of Cardiology (ESC) Guidelines for the Management of Arterial Hypertension.[9]

There is limited data on aspirin use in Turkey. The evaluation of the use of aspirin in actual clinical practice was first carried out in a study titled "Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study" (ASSOS trial).[10] The present study aims to investigate the use of aspirin in patients with and without HT, the association between aspirin and other CV risk factors, the outcomes of the physicians' adherence to current guidelines regarding their aspirin treatment preferences in clinical practice by using a large data set from the ASSOS trial carried out in Turkey.

METHODS

The ASSOS trial[10] is an observational, cross-sectional, national registry study. The study data were obtained between March 1, 2018, and June 31, 2018, from all consecutive patients who consulted to an outpatient cardiology clinic and were administered aspirin treatment. This non-randomized study was conducted by 30 cardiologists in 14 cities, and the patients were included regardless of why they were prescribed aspirin. Figure 1 shows the rates of distribution of patients based on geographical regions in Turkey. The study is not subjected to any diagnostic or treatment procedure and was approved by the Local Ethics Committee and registered at ClinicalTrials.gov under NCT03387384.

The 2016 European Guidelines on CV disease prevention in clinical practice[11] and 2016 United States Preventative Services Task Force Guidelines[12] were used to identify the indications for aspirin use. The patients included in the study were on aspirin therapy and their demographical and clinical data, CV risk factors, comorbidities, and concomitant medications were recorded. The duration of aspirin use, the role of aspirin (for PP and SP), and the specialization of the clinician who administered aspirin therapy were noted and evaluated. The risk for bleeding was determined by the HAS-BLED (HT, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR [international normalized ratio], elderly, drugs/alcohol concomitantly) score.[13] Major bleeding was defined as any bleeding that required a hospital stay, and minor bleedings included the following: minor gastrointestinal (GI) bleeding, gingival bleeding, nose bleeding, and hematuria.

Definition of Hypertension

Hypertension is defined as office systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg in the guidelines of the ESC and European Society of Hypertension, the International Society of Hypertensio, and the National Institute for Health and Care Excellence.[9,14,15]

In our study, we defined HT as having a history of HT diagnosed and/or treated with medication, an SBP greater than 140 mm Hg or a DPB greater than 90 mm Hg on at least 2 occasions, or receiving any antihypertensive drug. Patients on aspirin therapy were divided into 2 groups: those without HT (group 1) and those with HT (group 2). The groups were evaluated regarding their demographic, clinical, and CV risk factors, comorbidities, and medical treatments.

Statistical Analysis

Statistical analyses were conducted using the International Business Machines Statistical Package for the Social Sciences software version 21.0 (IBM Corp., Armonk, NY, USA). Fisher's exact test and Pearson's chi-square test were performed for categorical variables. Kolmogorov–Smirnov test was used to determine whether the variables are normally distributed. "Mean ± standard deviation" was used for variables with normal distribution, "median (25^{th}–75^{th} percentiles)" for variables without normal distribution, and "n (%)" for categorical variables. Mann–Whitney *U* test was used for comparing quantitative variables without normal distribution, while Student's *t*-test was used for comparing the means between 2 groups with normal distribution. A *P*-value < .05 was considered statistically significant.

RESULTS

A total of 5007 patients (1955 females, 39%) on Aaspirin therapy were enrolled in the study and were divided into 2 groups. Group 1 included 1540 patients (30.7%) without HT, and group 2 included 3467 patients (69.3%) with HT.

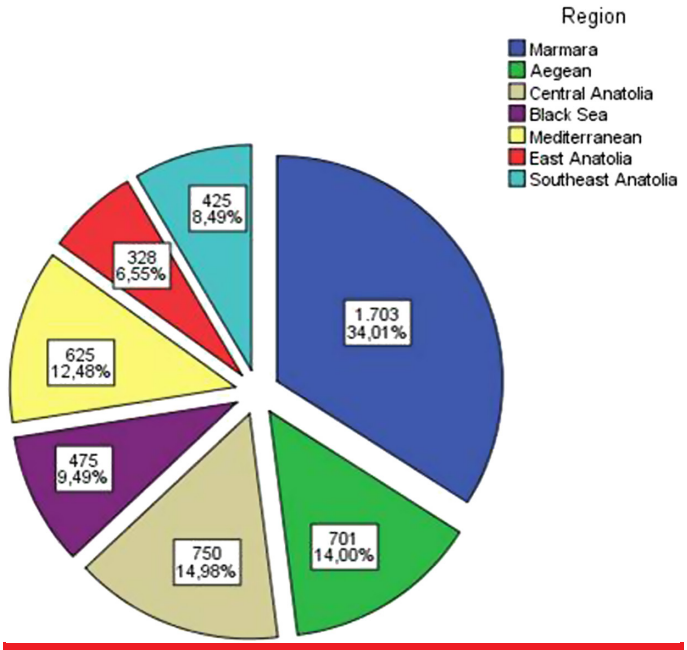

Figure 1. The number and rate of the patients chosen for the ASSOS trial in terms of geographical regions in Turkey.

HIGHLIGHTS

- A total of 69.3% of aspirin users were reported to have hypertension. Of the patients with hypertension, 30.2% were on aspirin treatment for primary prevention.
- An aspirin dose of 150 mg was mostly prescribed by internists and neurologists for the purpose of primary prevention to patients with hypertension.
- Low-dose aspirin (≤100 mg) was administered to patients with a known history of coronary artery disease by cardiologists for secondary prevention.

Comparison of Groups

Baseline characteristics of patients and comorbidities of the study population were demonstrated in Table 1. Patients with HT were significantly older than those without HT (59 ± 11 years, 64 ±11 years, $P < .001$). The ratio of female [435 (28.2%) vs. 1529 (43.8%) $P < .001$] and overweight patients [27.04 kg/m^2 (24.97-29.38); 28.34 kg/m^2 (25.71-31.59); $P < .001$] were higher in group 2 compared to group 1. The median values of SBP [120 mm Hg (110-130), 130 mm Hg (120-140); $P < .001$] and DPB measured during medical consultation [75 mm Hg (70-80), 80 mm Hg (70-85); $P < .001$] were higher in group 2 compared to group 1.

There was no significant difference between the 2 groups in terms of place of residence; however, the illiteracy rate in group 2 was more than the rate in group 1 [181 (11.8%); 609 (17.6); $P < .001$].

Group 2 had higher prevalence rates of diabetes mellitus (DM) [324 (21.7%); 1203 (34.7%); $P < 0.001$], heart failure [196 (12.7%); 546 (15.7%); $P = .005$], chronic renal failure (CRF) [35 (2.3%); 212 (6.1%); $P < .001$], hyperlipidemia (HL) [663 (43.1%), 1914 (55.2%); $P < .001$], chronic obstructive lung disease [128 (8.3%); 360 (10.4%); $P = .023$] compared to group 1. However, the rates of smoking [421 (27.3%); 700 (20.2%); $P < .001$] and alcohol consumption [123 (8.0%); 213 (6.1%); $P = .016$] were higher in group 1 than in group 2. No significant difference was found between the groups regarding atrial fibrillation, prior cerebrovascular events, and carotid artery disease.

The rates of coronary artery disease (CAD) [1123 (72.9%); 2301 (66.4%); $P < .001$] and previous percutaneous revascularization [666 (43.2%); 1296 (37.4%); $P < .001$] were significantly higher in group 1 than in group 2. Previous coronary artery bypass surgery rate was found to be higher in group 2 than in group 1 [262 (17%); 668 (19.3%); $P = .058$].

The Comparison of the Hypertensive Group and the Group without Hypertension in Terms of Geographical Regions

The data obtained through the ASSOS trial from 7 regions were investigated for each region in terms of the 2 groups (Table 2). Only in East Anatolia Region, no difference was found

Table 1. Baseline Characteristics and Comorbidities of the Study Population

	All Patients (n = 5007)	Patients Without HT (Group 1) (n = 1540)	Patients With HT (Group 2) (n = 3467)	P
Age (years)	62.15 ± 11.05	59 ± 11	64 ± 11	<.001
Gender (female), n (%)	1955 (39.0)	435 (28.2%)	1520 (43.8%)	<.001
BMI (kg/m^2)	27.7 (25.3-31.1)	27.04 (24.97-29.38)	28.34 (25.71-31.59)	<.001
Systolic blood pressure (mmHg)	130 (120-140)	120 (110-130)	130 (120-140)	<.001
Diastolic blood pressure (mmHg)	80 (70-80)	75 (70-80)	80 (70-85)	<.001
Smoking status Non-smokers Smokers Quitted smoking	2239 (44.7) 1121 (22.4) 1647 (32.9)	611 (39.7) 421 (27.3) 508 (33.0)	1628 (47.0)[a] 700 (20.2)[b] 1139 (32.9)	<.001
Place of residence Rural Urban	1072 (21.4) 3935 (78.6)	339 (22.0) 1201 (78.0)	733 (21.1) 2734 (78.9)	.255
Educational status No formal education Primary school Middle school High school University	790 (15.8) 2332 (46.6) 672 (13.4) 889 (17.8) 324 (6.5)	181 (11.8) 697 (45.3) 235 (15.3) 282 (18.3) 145 (9.4)	609 (17.6)[a] 1635 (47.2) 437 (12.6)[b] 607 (17.5) 179 (5.2)[b]	<.001
Alcohol use	336 (6.7)	123 (8.0)	213 (6.1)	.016
Heart failure	742 (14.8)	196 (12.7)	546 (15.7)	.005
Diabetes mellitus	1537 (30.7)	324 (21.7)	1203 (34.7)	<.001
Chronic renal failure	247 (4.9)	35 (2.3)	212 (6.1)	<.001
Hyperlipidemia	2577 (51.5)	663 (43.1)	1914 (55.2)	<.001
Coronary artery disease	3424 (68.4)	1123 (72.9)	2301 (66.4)	<.001
Prior CABG surgery	930 (18.6)	262 (17.0)	668 (19.3)	.058
Prior PCI	1962 (39.2)	666 (43.2)	1296 (37.4)	<.001
Carotid artery disease	201 (4.0)	62 (4.0)	139 (4.0)	.978
Prior CVE	351 (7.0)	93 (6.0)	258 (7.4)	.073
COPD history	488 (9.7)	128 (8.3)	360 (10.4)	.023

[a]Statistically higher than group 1; [b]statistically lower than group 1.
HT, hypertension; BMI, body mass index; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; CVE, cerebrovascular event; COPD; chronic obstructive pulmonary disease.

Table 2. Analysis of Patients With and Without Hypertension in Terms of Geographical Regions in Turkey

Marmara Region	**All Patients (n = 1703)**	**Patients Without HT (n = 445)**	**Patients With HT (n = 1258)**	***P***
Age (years)	63 ± 10	59 ± 11	65 ± 10	<.001
Gender (female), n (%)	1041 (61.1)	320 (71.9)	721 (61.1)	<.001
Aspirin dosage	1587 (93.2)	420 (94.4)	1167 (92.8)	.309
80-100 mg	71 (4.2)	13 (2.9)	58 (4.6)	
150 mg	45 (2.6)	12 (2.7)	33 (2.6)	
300 mg				
Primary prevention	420 (24.7)	79 (17.8)	641 (27.1)	<.001
Secondary prevention	1283 (75.3)	366 (82.2)	917 (72.9)	
Aegean Region	**All Patients (n = 701)**	**Patients Without HT (n = 241)**	**Patients With HT (n = 460)**	***P***
Age (years)	63 ± 10	61 ± 12	64 ± 10	<.001
Gender (female), n (%)	237 (33.8)	54 (22.4)	183 (39.8)	<.001
Aspirin dosage	683 (97.4)	233 (96.7)	450 (97.8)	.001
80-100 mg	8 (1.1)	0 (0)	8 (1.7)[a]	
150 mg	10 (1.4)	8 (3.3)	2 (0.4)[b]	
300 mg				
Primary prevention	170 (24.3)	52 (21.6)	118 (25.7)	.232
Secondary prevention	531 (75.7)	189 (78.4)	342 (74.3)	
Central Anatolia Region	**All Patients (n = 750)**	**Patients Without HT (n = 223)**	**Patients With HT (n = 527)**	***p***
Age (years)	61 ± 10	58 ± 11	63 ± 10	<.001
Gender (female), n (%)	296 (39.5)	52 (23.3)	244 (46.3)	<.001
Aspirin dosage	729 (97.2)	220 (98.7)	509 (96.6)	.174
80-100 mg	7 (0.9)	0 (0)	7 (1.3)	
150 mg	14 (1.9)	3 (1.3)	11 (2.1)	
300 mg				
Primary prevention	217 (28.9)	50 (22.4)	167 (31.7)	.011
Secondary prevention	533 (71.1)	173 (77.6)	360 (68.3)	
Black Sea Region	**All Patients (n = 475)**	**Patients Without HT (n = 200)**	**Patients With HT (n = 275)**	***p***
Age (years)	59 ± 10	58 ± 11	61 ± 11	0.001
Gender (female), n (%)	**159 (33.5)**	**53 (26.5)**	**106 (38.5)**	**.006**
Aspirin dosage	423 (89.1)	178 (89.0)	245 (89.1)	.775
80-100 mg	35 (7.4)	16 (8.0)	19 (6.9)	
150 mg	17 (3.6)	6 (3.0)	11 (4.0)	
300 mg				
Primary prevention	77 (16.2)	23 (11.5)	54 (19.6)	.018
Secondary prevention	398 (83.8)	177 (88.5)	221 (80.4)	
Mediterranean Region	**All Patients (n = 625)**	**Patients Without HT (n = 176)**	**Patients With HT (n = 449)**	***P***
Age (years)	63 ± 11	60 ± 12	64 ± 11	<.001
Gender (female), n (%)	279 (44.6)	60 (34.1)	219 (48.8)	.001
Aspirin dosage	549 (87.4)	163 (92.6)	383 (85.3)[b]	.045
80-100 mg	69 (11.0)	11 (6.3)	58 (12.9)[a]	
150 mg	10 (1.6)	2 (1.1)	8 (1.8)	
300 mg				
Primary prevention	165 (26.6)	34 (19.3)	132 (29.4)	.010
Secondary prevention	459 (73.4)	142 (80.7)	317 (70.6)	
East Anatolia Region	**All Patients (n = 328)**	**Patients Without HT (n = 114)**	**Patients With HT (n = 214)**	**p**
Age (years)	58 ± 12	57 ± 13	59 ± 12	.371
Gender (female), n (%)	128 (39.0)	37 (32.5)	91 (42.5)	.075
Aspirin dosage	325 (99.1)	111 (97.4)	214 (100)[a]	.058
80-100 mg	2 (0.6)	2 (1.8)	0 (0)	
150 mg	1 (0.3)	1 (0.9)	0 (0)	
300 mg				

(*Continued*)

Table 2. Analysis of Patients With and Without Hypertension in Terms of Geographical Regions in Turkey (*Continued*)

Primary prevention	177 (54.0)	49 (43.0)	128 (59.8)	.004
Secondary prevention	151 (46.0)	65 (57.0)	86 (40.2)	
Southeast Anatolia Region	**All Patients (n = 425)**	**Patients Without HT (n = 141)**	**Patients With HT (n = 284)**	***P***
Age (years)	61 ± 11	57 ± 11	64 ± 11	<.001
Gender (female), n (%)	194 (45.6)	54 (38.3)	140 (49.3)	.032
Aspirin dosage	378 (88.9)	132 (93.6)	246 (86.6)	.080
80-100 mg	26 (6.1)	4 (2.8)	22 (7.7)	
150 mg	21 (4.9)	5 (3.5)	16 (5.6)	
300 mg				
Primary prevention	147 (34.6)	41 (29.1)	106 (37.3)	.092
Secondary prevention	278 (65.4)	100 (70.9)	178 (62.7)	

[a]Statistically higher than patients without HT; [b]statistically lower than patients without HT.
HT, hypertension.

between the groups regarding age; the hypertensive group was found to be older than the other group for the remaining regions. According to the aspirin use in terms of gender, the rate of female gender was the highest in the Marmara Region with a rate of 61%, and the rate of male gender was statistically significantly higher in other regions. Low-dose aspirin use was found to be statistically significantly common in all regions.

Aspirin use for PP was found to be 24.7%, 24.3%, 28.9%, 16.2%, 26.6%, 54%, 34.6% in the regions of Marmara, Aegean, Central Anatolia, Black Sea, Mediterranean, East Anatolia, and Southeast Anatolia, respectively. No difference was found between hypertensive group and the group without HT in Souteast Anatolia and Aegean Regions regarding PP and SP. Aspirin use for primary prevention was found to be significantly higher in the hypertensive group compared to the group without HT in the Regions of Marmara [79 (17.8%); 641 (27.1%); $P < .001$], Central Anatolia [50 (22.4%); 167 (31.7%); $P = .011$], Black Sea [23 (11.5%); 54 (19.6%); $P = .018$], Mediterranean [34 (19.3%); 132 (29.4%); $P = .01$], and East Anatolia [49 (43%); 128 (59.8%); $P = .004$].

Aspirin Use in Hypertensive Group and Other Medical treatments

Aspirin use for PP was higher in group 2 compared to group 1 [328 (21.3%); 1046 (30.2%); $P < .001$]; however, aspirin use for SP was higher in group 1 than in group 2 [1212 (78.7%); 2421 (69.8%); $P < .001$]. The related data are shown in Table 3.

Group 2 patients were treated with 150 mg aspirin (n = 172, 5%) and group 1 patients with 80-100 mg aspirin (n = 1457, 94.6%). Aspirin treatment was mostly administered by internists (n = 226, 6.5%) followed by neurologists (n = 196, 5.7%) in group 2; however, the treatment was mostly preferred by cardiologists in group 1 (n = 1347, 87.5%). There was no significant difference between groups regarding the aspirin preference of other physicians (Table 3).

Table 4 demonstrates the data on the other medication used in the treatment of 5007 patients. The use of angiotensin-converting enzyme (ACE) inhibitors (n = 1367, 39.4%), angiotensin receptor blockers (ARBs) (n = 1308, 37.7%), calcium channel blockers, and diuretics were higher in group 2 patients than in group 1 patients. There was no difference between the groups in terms of beta-blocker, statin, and oral anticoagulation (warfarin and novel oral anticoagulants) use. Also, there was no significant difference between the groups regarding clopidogrel use, while the use of P2Y12 receptor blockers (ticagrelor and prasugrel) was found to be higher in group 1 than in group 2.

The use of non-steroidal anti-inflammatory (NSAI) drugs [81 (5.3%); 451 (13%); $P < .001$], proton pump inhibitors (PPI) [596 (38.7%); 1485 (42.8%); $P = .006$], and diabetes medications (oral and insulin drugs) higher in group 2 than in group 1. HAS-BLED scores were higher in group 2 when compared to group 1 [1 (1-2); 2 (1-2); $P < .001$]. There was no difference between the groups with respect to major bleedings, while the prevalence of minor bleedings was higher in group 2 than in group 1 [158 (10.3%); 476 (13.7%); $P = .001$].

DISCUSSION

In the subgroup analysis of the hypertensive group of ASSOS trial, a total of 69.3% of aspirin users were reported to have HT, and of the patients with HT, 30.2% were on aspirin treatment for PP. The hypertensive group consisted of older and heavier patients and the percentage of females was also higher in this group when compared to the group without HT. The other main findings of our study were as follows: (1) according to the geographical analysis, aspirin use for PP was found to be 54% in East Anatolia Region, and 59.8% of patients with HT were found to be on aspirin treatment for PP, (2) an aspirin dose of 150 mg was mostly prescribed by internists and neurologists for the purpose of PP to patients with HT, (3) history of CAD and prior percutaneous coronary intervention (PCI) was mostly observed in the group without HT, (4) hypertensive group had multiple comorbidities such as DM, HL, CRF, COPD, and heart failure, and (5) low-dose aspirin (≤100 mg) was administered to patients with a known history of CAD and prior PCI by cardiologists for SP.

CV disease continues to be the leading cause of death among adults.[16,17] The risk for a subsequent MI, stroke, and vascular death has had a statistically significant clinical decrease in an extensive range of patients who previously had an occlusive CV event.[18,19] Aspirin has long been used as the most trusted medicine for this purpose.[20]

Table 3. Patients' Preferences and Aspirin Dosage and Complications in Patients With and Without Hypertension

	All Patients (n = 5007)	Patients Without HT (Group 1) (n = 1540)	Patients With HT (Group 2) (n = 3467)	*P*
Aspirin dosage	4671 (93.3)	1457 (64.9)	3214 (92.7)[b]	.007
80-100 mg	218 (4.4)	46 (3.0)	172 (5.0)[a]	
150 mg	118 (2.4)	37 (2.4)	81 (2.3)	
300 mg				
Primary prevention	1374 (27.4)	328 (21.3)	1046 (30.2)	<.001
Secondary prevention	3633 (72.6)	1212 (78.7)	2421 (69.8)	
Aspirin preference	4167 (83.2)	1347 (87.5)	2820 (81.3)[b]	<.001
Cardiology	259 (5.2)	63 (4.1)	196 (5.7)[a]	
Neurology	265 (5.3)	39 (2.5)	226 (6.5)[a]	
Internal medicine	194 (3.9)	53 (3.4)	141 (4.1)	
Cardiovascular surgery	61 (1.2)	21 (1.4)	40 (1.2)	
Family physician	24 (0.5)	9 (0.6)	15 (0.4)	
Patient preference	37 (0.7)	8 (0.5)	29 (0.8)	
Others				
NSAIDs	528 (10.5)	111 (7.2)	417 (12.0)	<.001
HAS-BLED score	1 (1-2)	1 (1-2)	2 (1-2)	<.001
Major bleeding	72 (1.4)	18 (1.2)	54 (1.6)	.286
Minor bleeding	634 (12.7)	158 (10.3)	476 (13.7)	.001

[a]Statistically higher than group 1; [b]statistically lower than group 1.
HT, hypertension; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 4. Other Medical Treatments in Patients With and Without Hypertension on Aspirin

	All Patients (n = 5007)	Patients Without HT (Group 1) (n = 1540)	Patients with HT (Group 2) (n = 3467)	*P*
ACEi	1685 (33.7)	318 (20.6)	1367 (39.4)	<.001
ARB	1426 (28.5)	118 (7.7)	1308 (37.7)	<.001
Beta blockers	3483 (69.6)	1056 (68.6)	2427 (70.0)	.310
Non-dihydropyridine CCB	301 (6.0)	60 (3.9)	241 (7.0)	<.001
Dihydropyridine CCB	849 (17.0)	53 (3.4)	796 (23.0)	<.001
Digoksin	198 (4.0)	76 (4.9)	122 (3.5)	.018
Statin	2561 (51.1)	785 (51.0)	1776 (51.2)	.869
Furosemid	561 (11.2)	127 (8.2)	434 (12.5)	<.001
Hydrochlorothiazide	1042 (20.8)	101 (6.6)	941 (27.1)	<.001
NSAIDs	532 (10.6)	81 (5.3)	451 (13.0)	<.001
OAD	1141 (22.8)	218 (14.2)	932 (26.6)	<.001
Insulın therapy	437 (8.7)	82 (5.3)	355 (10.2)	<.001
Clopidogrel	1067 (21.3)	315 (20.5)	752 (21.7)	.324
Ticagrelor	304 (6.1)	120 (7.8)	184 (5.3)	.001
Prasugrel	128 (2.6)	54 (3.5)	74 (2.1)	.005
Warfarin, NOACs	251 (5,0)	78 (5,1)	173 (5.0)	.911
PPIs	2081 (41.6)	596 (38.7)	1485 (42.8)	.006

ACEi, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CCB, calcium channel blockers; NSAIDs, non-steroidal anti-inflammatory drugs; OAD, oral antidiabetic drug; NOACs, novel oral anticoagulants; PPI, proton pump inhibitors.

There is a limited number of small-scale studies investigating the effect of aspirin on blood pressure. In these studies, aspirin did not cause a significant decrease in blood pressure.[21,22] Although aspirin has many effects that theoretically can help lower blood pressure, it is not medically used to reduce blood pressure. Considering the immense importance of the prevention of adverse CV events in the management of patients with arterial HT, so many hypertensive patients use aspirin. Our large-scale study revealed that 69.3% of all the patients who are on aspirin therapy also have HT.

Aspirin therapy is essential in the SP of CV disease.[20] Apparently, the benefit of aspirin is well acknowledged and the use of antiplatelet therapy for SP has been supported by several studies.[23,24] Prophylactic use of aspirin in individuals without a known CV disease was not

encouraged in the present European guidelines on the prevention of CV disease as major bleeding is a far riskier issue when compared to the minor reduction in major adverse cardiac event rates.[11] According to the 2018 ESC Guidelines for the Management of Arterial Hypertension,[9] aspirin use is not supported for PP in hypertensive patients without CV disease (class III, level A). Aspirin was indicated not to reduce stroke and CV events in hypertensive patients without prior CV disease when compared to placebo in PP.[25] Yet in the same guideline,[9] vascular events were found to lower by 4.1% with antiplatelet therapy in patients with increased BP levels in SP.[25] And the benefit of Aspirin therapy in hypertensive patients may outweigh the harm that it may cause in SP.[11,25]

The 2019 American College of Cardiology/American Heart Association Guideline on the Primary Prevention of Cardiovascular Disease does not recommend routine low-dose aspirin (75-100 mg orally daily) treatment for people aged >70 years for PP of atherosclerotic CV disease (class III, level B). Low-dose aspirin use is also not recommended in the same guideline for PP in adults with a high risk of bleeding, regardless of their age (class III, level C). The guideline also suggests that low-dose aspirin (75-100 mg orally daily) may be considered for PP in adults aged between 40 and 70 without any risk of bleeding (class IIb, level A).[26]

In Turkey, there is limited data on aspirin use. In our subgroup analysis of the ASSOS trial, hypertensive patients on aspirin therapy were of advanced age and had multiple CV risk factors. Remarkably, aspirin was prescribed particularly by internists and neurologists for PP in hypertensive patients with multiple CV risk factors. The preference of the physicians was probably affected by their prioritizing CV risk factors. In a study by Çelik et al.[27,28] aspirin was shown to be prescribed by other physicians more for PP independent of HT when compared to cardiologists and cardiovascular surgeons. The group without HT (30%) were younger and had a history of CAD and expectedly, cardiologists preferred to prescribe low-dose aspirin for SP. The use of other antiaggregant drugs was also higher among the patients in this group.

There is no clear data on the optimal daily dose in long-term aspirin use. Doses ranging from 75 to 325 mg/day were evaluated in various studies. In one of these meta-analyses, the Antithrombotic Trialists' Collaboration reported that the benefits of all doses of aspirin from 75 to 1300 mg/day were alike.[18] On the contrary, the bleeding risk, particularly GI bleeding, got elevated when the dose went above 325 mg/day. Our research revealed that various physicians in different fields chose to treat their patients with their own specific doses. We also reported that aspirin having been used for many years in patients with multiple CV risk factors is prescribed by physicians quite easily.

In this subgroup analysis of the ASSOS trial, the hypertensive patient group using aspirin was older, heavier, and had a higher percentage of female gender compared to the group of patients without HT. Çelik et al[27] reported a greater probability of aspirin administration to female patients independent of HT for PP when compared to male patients in ASSOS trial subgroup analysis on proper aspirin use in clinical cardiology. Female gender was also found to be an independent predictor of inappropriate use of aspirin for PP.[27]

Similarly, our study revealed that having multiple comorbidities such as DM, HL, CRF, COPD, and heart failure increased the probability of being prescribed aspirin independent of guidelines in hypertensive patients using aspirin even if they had no known history of CAD or prior PCI. Some studies suggest that the occurrence of CV events despite regular use of aspirin is the result of insufficient treatment[29] and a dose change should be made in clinical use. For instance, a meta-analysis carried out in 2018 assessed the effect of the patients' body weight on the efficacy and safety of aspirin by using the patient data obtained from randomized trials on aspirin use for PP and SP.[30] In this analysis, the risk of a major CV event was found to be lower in patients with a bodyweight of ≤70 kg who were on low-dose (75-100 mg) aspirin. Also, aspirin was found to be more effective in patients weighing ≥70 kg when administered in higher doses (≥325 mg). There is no recommendation for individual dosing of aspirin currently in the guidelines. Evidently, more large-scale studies are needed on this matter.

Acetylsalicylic acid (aspirin) is available in 80-100-150 and 300 mg formulations in Turkey. In the subgroup analysis of the hypertensive group of ASSOS trial, no significant difference was found regarding 300 mg aspirin use between the hypertensive group and the group without HT, and 150 mg daily oral use of aspirin was preferred in the hypertensive group. This dose is most likely the daily intake of aspirin that is mostly preferred by internists and neurologists. In this study, no significant difference was found regarding (major) bleedings that require hospitalization between the hypertensive group and the group without HT. Hypertensive patients were found to have higher rates of HAS-BLED bleeding score, NSAID use, and as a result, minor bleeding compared to those without HT. Although the rate of PPI use was higher in the hypertensive group, it was more likely that adverse effects related to advanced age, comorbid factors, and multiple drug intake resulted in negative outcomes in this group.

In the subgroup analysis of the hypertensive group of ASSOS trial, despite the recommendations of the guidelines, hypertensive patients' advanced age and multiple CV risk factors seemed enough for the easy aspirin prescription by physicians even if these patients had no known history of CAD. Yet, benefits and risks should be well evaluated in aspirin use. Awareness should be raised among healthcare workers and in society about aspirin and multiple drug intake.

Limitations of Study

The Appropriateness of Aspirin Use in Medical Outpatients: A Multicenter, Observational Study is a remarkable study for its evaluation of aspirin use in actual clinical practice in Turkey for the first time. One of the main limitations of the ASSOS trial is the cross-sectional design of the study. Another one is that the study did not report safety and efficacy outcomes. Another limitation is the study population which was determined considering 7 regions of Turkey instead of taking the

population density of Turkey into account. The study solely included cardiology clinics, so the outcomes do not represent the whole healthcare centers such as primary care and other specialties. For that matter, the appropriate use of aspirin might not have been accurately evaluated for its use in general practice and might have been overestimated regarding the findings of the study.

CONCLUSIONS

This study is the first observational study that reports the aspirin use of HT patients in Turkey under the perspective of ASSOS trial data. According to the current study, 30% of HT patients are on aspirin treatment despite the guidelines not recommending aspirin use. The dose selection of aspirin was also shown to depend completely on the clinician. Multiple drug use, drug interactions, and possible complications should not be underestimated by the clinicians. Aspirin has long been on the market and prescribed easily by clinicians which makes it look totally harmless; however, it is critical that clinicians closely follow the latest guidelines and conducted studies. We believe our study will raise awareness among the clinicians in our country regarding this matter.

Ethics Committee Approval: The study is not subjected to any diagnostic or treatment procedure and was approved by the Local Ethics Committee and registered at ClinicalTrials.gov under NCT03387384.

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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