Inappropriate combination of warfarin and aspirin

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Abstract

Objective: A combination of warfarin and aspirin is associated with increased bleeding compared with warfarin monotherapy. The aim of the study was to investigate the incidence and appropriateness of the combination of warfarin and aspirin in patients with atrial fibrillation (AF) or mechanical heart valve (MHV).

Methods: This cross-sectional study included consecutive patients with AF or MHV on chronic warfarin therapy (>3 months) without acute coronary syndrome or have not undergone a revascularization procedure in the preceding year. Medical history, concomitant diseases, and treatment data were acquired through patient interviews and from hospital records.

Results: Three hundred and sixty patients (213 with AF, 147 with MHV) were included. In those with AF, a significantly higher warfarin-aspirin combination was observed with concomitant vascular disease (38.8% vs. 14.6%), diabetes (36.6% vs. 16.3%), statin therapy (40% vs. 16.9%), left ventricular systolic dysfunction (33.3% vs. 17.5%) ($p<0.05$ for all). The use of combination therapy was similar between different CHADS-VASc scores. In patients with MHV, higher combination therapy was observed in males (41% vs. 26.7% in females; $p=0.070$), concomitant vascular disease (47.8% vs. 29.8%; $p=0.091$), and AF (56.3% vs. 29.8%; $p=0.033$). Independent predictors of warfarin-aspirin combination were concomitant vascular disease, diabetes, and (younger) age in patients with AF and were concomitant AF and male sex in patients with MHV. Interestingly, the incidence of combination therapy was found to increase with a higher HAS-BLED score in both patients with AF and MHV ($p<0.001$).

Conclusion: The combination of warfarin and aspirin was found to be prescribed to patients with AF mainly for the prevention of cardiovascular events, for which warfarin monotherapy usually suffices. On the other hand, co-treatment with aspirin appeared to be underused in patients with MHV. *(Anatol J Cardiol 2016; 16: 189-96)*

Keywords: warfarin, aspirin, atrial fibrillation, heart valve prosthesis

Introduction

The number of patients on oral anticoagulant (OAC) therapy is increasing with the age of the general population. Atrial fibrillation (AF) and mechanical heart valve (MHV) replacement are two main indications for warfarin therapy in addition to venous thromboembolism, intracardiac thrombus, recurrent stroke, and others. Many patients are being prescribed aspirin in addition to warfarin for the prevention of cardiovascular events or simply a better antithrombotic effect. The combination of antiplatelet therapy with warfarin leads to a 1.5 to 2-fold increase in bleeding episodes compared with warfarin therapy alone (1-3) and is not recommended in patients with AF without acute coronary syndrome (ACS) or who have not undergone a revascularization procedure in the preceding year (4, 5). However, this combination is generally recommended in patients with MHV with low bleeding risk (6-8). In this study, we aimed to find the real-world incidence of a combination of warfarin and aspirin in patients with AF or MHV without recent ACS or who have not undergone a revascularization procedure and determine whether this combination therapy is justified according to latest practice guidelines (6-10).

Methods

Patients and definitions

The study was a cross-sectional study. The study participants were consecutive patients on warfarin therapy for more than 3 months who presented to the outpatient department of cardiology at Kocaeli Derince Training and Research Hospital. Patients who had AF or MHV or both were included in the study. Patients who had ACS or underwent percutaneous coronary intervention (PCI) or a revascularization procedure involving the peripheral arteries in the preceding year were excluded.

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Because the vast majority of patients attend their routine follow-up once a month, a data collection time of 3 months was considered adequate for a single-center study.

Medical history, concomitant diseases, and treatment data were obtained through patient interviews or from hospital records. Major bleeding was defined as intracranial bleeding or any bleeding requiring transfusion under warfarin therapy. Other types of bleeding under warfarin therapy were classified as minor bleeding. Cerebrovascular accident (CVA) was defined as transient or permanent neurologic deficit of thromboembolic etiology. Coronary artery disease (CAD) was defined as documented history of myocardial infarction or the presence of more than 50% diameter stenosis of a coronary artery on coronary angiography. Peripheral artery disease (PAD) was defined as angiographically or noninvasively (with ultrasound, computed tomography, magnetic resonance imaging) documented critical stenosis in the carotid, renal, or upper or lower extremity arteries. Vascular disease was defined as disease of either the coronary or peripheral arteries.

Blood samples for international normalized ratio (INR) were drawn as a part of routine control. Therapeutic INR ranges were 2.0-3.0 for patients with AF and aortic valve replacement (AVR) and 2.5-3.5 for patients with mitral valve replacement (MVR) and AVR plus AF, as described by the guidelines (6-10). Echocardiography was performed for patients without recent assessment. Left ventricular (LV) systolic dysfunction was accepted as an ejection fraction less than 40%. CHADS-VASc [Congestive heart failure, Hypertension, Age≥75 (doubled), Diabetes, Stroke (doubled), Vascular disease, Age 65-74 years, Sex category (female)] and HAS-BLED [Hypertension, Abnormal liver/kidney function (1 point each), Stroke, Bleeding history, Labile INR, Elderly (>65 years), Drugs/alcohol (1 point each)] scores were calculated at the time of the interview. Although the HAS-BLED score was described for AF, it was also used in MHV replacement to estimate bleeding risk (11). This study was approved by the local Ethics Committee (Clinical Research Ethics Committee of the Faculty of Medicine of Kocaeli University, number: KOÜ KAEK 2013/20). Patients who did not give written informed consent were not included in the study.

Statistical analysis

Continuous variables were presented as means ± standard deviations and compared using the student t-test. INR values and duration of warfarin therapy did not show normal distribution and were presented as median (25-75 percentiles) and compared using the Mann-Whitney U test. Categorical variables were presented as numbers (percentages) and compared using the chi square or Fisher's exact test. A two-sided p value of <0.05 was considered statistically significant. Logistic regression analysis (LRA) was performed to determine independent correlates of bleeding episodes and warfarin–aspirin combination. A stepwise model with backward selection method was used, and p values of <0.050 and of >0.100 were selected for inclusion to and exclusion from the next step, respectively. Results were tabulated as odds ratio (OR) and 95% confidence intervals (CI). Statistical Package for the Social Sciences (SPSS for Windows, Version 11.0, SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Results

Study patients

A total of 383 patients who had been using warfarin for more than 3 months applied between December 2013 and March 2014 in this cross sectional study. Fourteen patients with documented ACS in the preceding year, 7 of whom underwent ad-hoc PCI, were excluded. Two patients with deep venous thrombosis, 1 patient with recent pulmonary embolism, 3 patients with LV thrombus, 1 patient with advanced heart failure and sinus rhythm, 1 patient with a history of CVA and sinus rhythm, and 1 patient with a history of Fontan procedure were also excluded. There were 5 patients (4 patients with AF, 1 with MHV) without recent ACS or a revascularization procedure who used clopidogrel in addition to warfarin. They were not excluded but categorized in the warfarin-aspirin group for the purpose of the study. One patient with AF and biological aortic valve prosthesis was categorized in the AF group. Finally, the study participants comprised 360 patients.

AF and MHV replacement constituted a vast majority (374/383, 97.7%) of presenting cases on chronic warfarin therapy. AF was more common than MHV replacement as an indication for warfarin therapy (Fig. 1). The mean age of the patients was 64±12 years, 60% were female, 62.2% had hypertension, 16.9% had diabetes, 16.1% had CAD, 11.9% had a history of cerebrovascular event (CVA), and 5.8% had PAD (Table 1). Patients with AF were expectedly older than those with MHV. The median duration of warfarin therapy was 2.8 years (Table 2) and was significantly longer in patients with MHV replacement (median, 4.3 years) compared with patients with AF (median, 2.0 years). INR was within the therapeutic range in 43.6% of all patients and

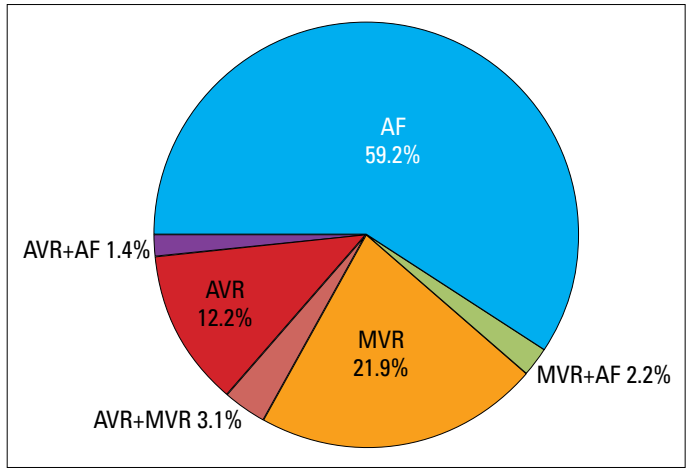

Figure 1. Indications for warfarin therapy

Table 1. Baseline characteristics of patients on chronic warfarin therapy

	All patients n=360	Patients with AF n=213	Patients with MHV n=147	*P*
Demographics				
Age, years	64±12	68±11	59±13	<0.001
Age>65 years	192 (53.3)	138 (64.8)	54 (36.7)	<0.001
Age>75 years	65 (18.1)	55 (25.8)	10 (6.8)	<0.001
Male sex	144 (40)	83 (39)	61 (41.5)	0.630
Hypertension	224 (62.2)	146 (68.5)	78 (53.1)	0.003
Diabetes	61 (16.9)	41 (19.2)	20 (13.6)	0.161
CAD	58 (16.1)	41 (19.2)	17 (11.6)	0.051
History of PCI	15 (4.2)	12 (5.6)	3 (2)	0.094
History of CABG	26 (7.2)	13 (6.1)	13 (8.8)	0.324
PAD	21 (5.8)	14 (6.6)	7 (4.8)	0.471
Vascular disease	72 (20)	49 (23)	23 (15.6)	0.086
History of CVA	43 (11.9)	28 (13.1)	15 (10.2)	0.398
Concomitant medications				
Aspirin	93 (25.8)	45 (21.1)	48 (32.7)	0.014
Clopidogrel	5 (1.4)	4 (1.9)	1 (0.7)	0.340
RAS blocker	204 (56.8)	141 (66.2)	63 (42.9)	<0.001
Beta blocker	206 (57.2)	125 (58.7)	81 (55.1)	0.499
Diltiazem or Verapamil	52 (14.4)	41 (19.2)	11 (7.5)	0.002
Dihydropyridine CCB	36 (10)	23 (10.8)	13 (8.8)	0.543
Digoxin	62 (17.2)	37 (17.4)	25 (17)	0.928
Diuretic	127 (35.3)	81 (38)	46 (31.3)	0.189
Statin	47 (13.1)	30 (14.1)	17 (11.6)	0.485
Proton pump inhibitor	35 (9.7)	19 (8.9)	16 (10.9)	0.536

CABG - coronary artery bypass grafting; CAD - coronary artery disease; CCB - calcium channel blocker; CVA - cerebrovascular accident; PAD - peripheral artery disease; PCI - percutaneous coronary intervention; RAS - renin-angiotensin system

did not differ between AF (43.2%) and MHV (44.2%). Minor bleeding events were more common in patients with MHV, as observed by a higher level of anticoagulation (median INR, 2.4 vs. 2.2) and a higher incidence of aspirin combination. There was no difference in major bleeding events. Renin-angiotensin system blockers and nondihydropyridine calcium channel blockers (diltiazem or verapamil) were more common in patients with AF. Patients with AF were found to have significantly more LV systolic dysfunction, atrial dilatation, and moderate to severe valvular disease (Table 3).

Bleeding episodes

Minor bleeding was described by 111 patients (50 patients with AF, 61 patients with MHV), and major bleeding was observed in 13 patients (5 patients with AF, 8 patients with MHV) under anticoagulant therapy. Female sex (66.7% vs. 57%; p=0.085) and MHV replacement (55% vs. 34.5%; p<0.001), especially MVR

Table 2. Details of chronic warfarin therapy

	All patients n=360	Patients with AF n=213	Patients with MHV n=147	*P*
Time on warfarin therapy, years	2.8 (2.5-4.0)	2 (1.2-2.5)	4.3 (2.0-6.0)	<0.001
INR	2.3 (1.9-2.8)	2.2 (1.8-2.8)	2.4 (2.0-2.9)	0.024
INR within therapeutic range	157 (43.6)	92 (43.2)	65 (44.2)	0.875
History of minor bleeding	111 (30.8)	50 (23.5)	61 (41.5)	<0.001
History of major bleeding	13 (3.6)	5 (2.3)	8 (5.4)	0.122

INR - international normalized ratio

Table 3. Echocardiographic findings

	All patients n=360	Patients with AF n=213	Patients with MHV n=147	*P*
LV systolic dysfunction	47 (13.1)	36 (16.9)	11 (7.5)	0.009
LV hypertrophy	42 (11.7)	28 (13.1)	14 (9.5)	0.412
Moderate to severe valvular disease	56 (15.6)	47 (22.1)	9 (6.1)	<0.001
Left atrial dilation	124 (34.4)	94 (44.1)	30 (20.4)	<0.001
Pulmonary hypertension	34 (9.4)	18 (8.4)	16 (10.9)	0.747

LV - left ventricular

(38.7% vs. 22.1%; p=0.001), were more common in patients with a history of minor bleeding compared with those without bleeding history. On the other hand, patients with a history of major bleeding were older (71±10 vs. 64±12 years; p=0.043) and more likely to have hypertension (92.3% vs. 61.1%; p=0.023) and AVR (38.5% vs. 15.9%; p=0.032) compared with those without major bleeding. Increasing age appeared to be a significant factor in major bleeding, because 10 of 13 patients (76.9%) were over 65 years and 6 of 13 patients (46.2%) were over 75 years of age. Although it did not reach statistical significance, there was a trend toward increased use of proton pump inhibitors in patients with a history of major bleeding (23.1% vs. 9.2%; p=0.098).

The warfarin-aspirin combination

Of all patients, 25.8% (93 patients) were under combination therapy. Patients with MHV received combination therapy more frequently than those with AF. Combination therapy patients were generally male and diabetic, more likely to have concomitant vascular disease or MHV (Table 4), and more likely to receive concomitant statin treatment (20.4% vs. 10.5%; p=0.014) than warfarin monotherapy patients. A history of bleeding episodes was not statistically different between the two groups, although both minor and major bleedings were observed more

Table 4. Comparison of patients on warfarin monotherapy vs. the warfarin-aspirin combination

	Warfarin monotherapy n=267	Warfarin-aspirin combination n=93	*P*
Age, years	64±12	63±12	0.220
Male	97 (36.3)	47 (50.5)	0.016
Hypertension	167 (62.5)	57 (61.3)	0.830
Diabetes	29 (14.6)	22 (23.7)	0.045
AF	175 (65.5)	54 (58.1)	0.197
MHV replacement	99 (37.1)	48 (51.6)	0.014
History of PCI	91 (3.4)	60 (6.5)	0.200
History of CABG	15 (5.6)	11 (11.8)	0.046
CAD	32 (12)	26 (28)	<0.001
PAD	8 (3)	13 (14)	<0.001
Vascular disease	40 (15)	32 (34.4)	<0.001
History of CVA	31 (11.6)	12 (12.9)	0.741
History of minor bleeding	77 (28.8)	34 (36.6)	0.194
History of major bleeding	8 (3.0)	5 (5.4)	0.327

AF - atrial fibrillation; CABG - coronary artery bypass grafting; CAD - coronary artery disease; CVA - cerebrovascular accident; MHV - mechanical heart valve; PAD - peripheral artery disease; PCI - percutaneous coronary intervention

frequently in the combination group numerically. We analyzed patients with AF and MHV separately with regard to combination therapy, because the two conditions warrant different antithrombotic management.

Patients with atrial fibrillation

Distribution of patients with AF according to the CHADS-VASc score was relatively symmetrical (Fig. 2), majority of patients being within the score range of 2 to 4. Seven patients (3.3%) who had a risk score of 0 were found to be prescribed warfarin unnecessarily and 2 patients (28.6%) in that group received concomitant aspirin. In addition, 20% (6/30) of patients with a risk score of 1 were receiving concomitant aspirin, whereas one of the two agents would generally suffice. It is remarkable that co-treatment with aspirin was similar among different CHADS-VASc risk scores (p=0.255), indicating that aspirin was given to patients with AF on warfarin therapy regardless of the thromboembolic risk. Bleeding risk of the patients according to the HAS-BLED score is shown in Figure 2. The distribution of the HAS-BLED score was relatively symmetrical, majority of patients falling in the risk score range of 2 to 3. However, there was significant discrepancy between the calculated bleeding risk and concomitant aspirin treatment. Indeed, the incidence of concomitant aspirin treatment increased significantly with higher HAS-BLED risk scores, i.e., 0% (0/7), 6.3% (2/32), 11.3% (8/71), 24.2% (16/66), 48% (12/25), and 63.6% (7/11) for risk scores 0, 1, 2, 3, 4, and 5 respectively (p<0.001).

Subgroups of patients with AF according to concomitant disease are shown in Figure 3. Combination therapy usage did not differ among elderly, male, or hypertensive patients compared with others. However, patients with diabetes used combination therapy more frequently than those without diabetes [15/41 (36.6%) vs. 28/172 (16.3%); p=0.004]. In addition, both patients with CAD [17/41 (41.5%) vs. 26/172 (15.1%); p<0.001] and PAD [7/14 (50%) vs. 36/199 (18.1%); p=0.004] and thus patients with vascular disease [19/49 (38.8%) vs. 24/164 (14.6%); p<0.001] were receiving combination therapy more frequently. Patients with AF and LV systolic dysfunction were prescribed a combination of warfarin-aspirin more frequently than those with AF and normal systolic function [12/36 (33.3%) vs. 31/177 (17.5%); p=0.031]. Statin users were another target group for the addition of aspirin to warfarin therapy because 40% (12/30) of statin users were receiving combination therapy, whereas only 16.9% (31/183) of patients without statin therapy were receiving combination therapy (p=0.004). Remarkably, patients who had a history of minor bleeding were using concurrent warfarin–aspirin therapy more commonly compared with those without a history of minor bleeding [15/50 (30%) vs. 28/163 (17.2%); p=0.048], and 40% of patients with a history of major bleeding (2/5) were still using warfarin and aspirin together, whereas 19.7% of patients without a history of major bleeding (41/208) were using this combination (p=0.264). The difference did not reach statistical significance because of limited number of cases.

A model that included variables such as age, sex, hypertension, diabetes, CAD, vascular disease, a history of CVA, history of bleeding, statin therapy, and LV systolic dysfunction was con-

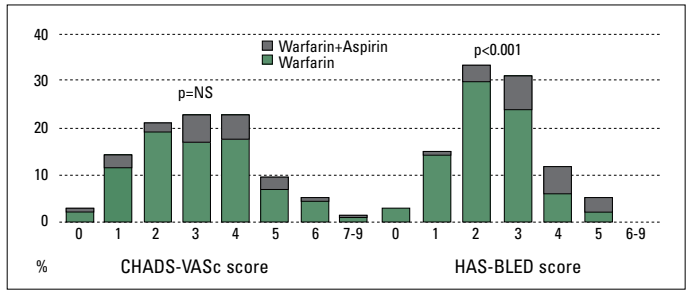

Figure 2. Distribution of patients with AF according to CHADS-VASc and HAS-BLED scores

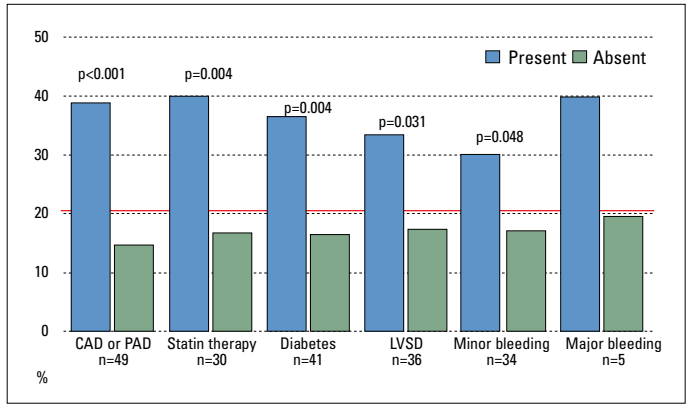

Figure 3. Incidence of the warfarin-aspirin combination according to the co-morbidities of patients with AF. The pink line indicates the incidence of the warfarin-aspirin combination in all patients with AF

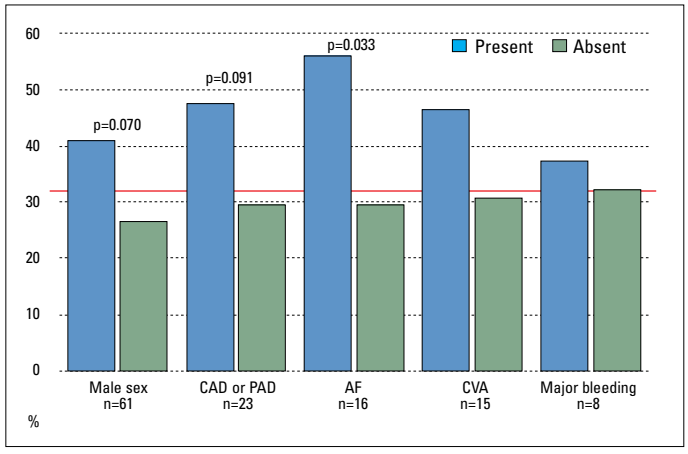

Figure 4. Incidence of the warfarin-aspirin combination according to the co-morbidities of patients with MHV. The pink line indicates the incidence of the warfarin-aspirin combination in all patients with MHV

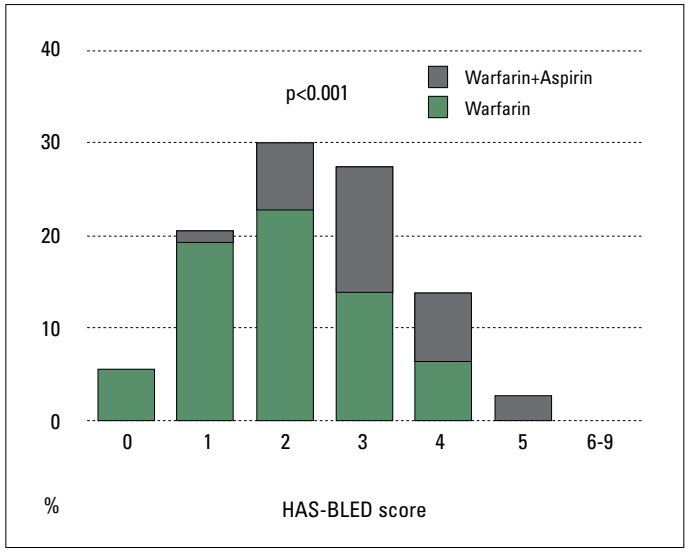

Figure 5. Distribution of patients with MHV according to the HAS-BLED score

structed in LRA. The accuracy of the model was 79.3%. Independent correlates of warfarin-aspirin therapy in patients with AF were found to be vascular disease (OR, 4.0; 95% CI, 1.9-8.5; p<0.001), diabetes (OR, 2.6; 95% CI, 1.2-5.8; p=0.02), and age (OR, 0.97; 95% CI, 0.94-1.00; p=0.065), although the latter had borderline significance. Results showed that aspirin was preferably added to warfarin in relatively younger patients with diabetes or vascular disease.

Patients with mechanical heart valve

Male patients with MHV tended to use aspirin in addition to warfarin more frequently [25/61 (41%) vs. 23/86 (26.7%); p=0.070], whereas combination treatment was similar in patients with diabetes compared with those without diabetes and patients with hypertension compared with those without hypertension (Fig. 4). Similar to patients with AF, the presence of vascular disease numerically increased the incidence of the warfarin-aspirin combination from 29.8% (37/124) to 47.8% (11/23) (p=0.091). However, only half of the patients with MHV and known vascular disease received the warfarin-aspirin combination. Besides, only 7 of 15 (46.7%) patients with MHV with a history of CVA were receiving combination therapy that did not differ from patients without CVA history (41/132, 31.1%; p=0.251). As was the case with patients with AF, 3 of 8 patients (37.5%) with a history of major bleeding continued to use combination therapy. On the other hand, patients with MHV and AF were more frequently prescribed aspirin in addition to warfarin [9/16 (56.3%) vs. 39/131 (29.8%); p=0.033). Figure 5 shows the distribution of antithrombotic therapy according to the HAS-BLED score. The situation was almost exactly the same as AF. The proportion of the warfarin-aspirin combination increased with increasing bleeding risk, i.e., 0% (0/8), 6.7% (2/30), 25% (11/44), 50% (20/40), 55% (11/20), and 100% (4/4) for risk scores 0, 1, 2, 3, 4, and 5, respectively (p<0.001).

LRA, which included variables age, sex, hypertension, diabetes, vascular disease, AVR, MVR, and AF, (model accuracy 70%) revealed that concomitant AF (OR, 3.4; 95% CI, 1.2-10.1; p=0.026) and male sex (OR, 2.1; 95% CI, 1.0-4.3; p=0.046) were independent correlates of the warfarin-aspirin combination. Results showed that the decision to add aspirin to warfarin in patients with MHV was probably related to the desire for a better antithrombotic effect.

Discussion

We have found a remarkable incidence of warfarin-aspirin combination in patients with AF or MHV or both. In general, warfarin-aspirin combination seemed inappropriate for patients with AF whereas it seemed inadequate for patients with MHV. In addition, the assessment of bleeding risk with regard to antithrombotic therapy was unfortunately below the standards of patient care indicated by clinical practice guidelines.

AF (59.3%) was the most common indication for chronic warfarin therapy, followed closely by MHV (38.4%) and other indications were presented rarely in this study of real world practice. In comparison, a large community-based cohort (12) reported that AF (48%) was the leading indication of warfarin treatment, followed by venous thromboembolism (27%), MHV (11%), and prior stroke or transient ischemic attack (7%). The proportion of patients with MHV was high in our work probably because of a higher prevalence of rheumatic heart disease in our country compared with the western world (13). Recent Atrial Fibrillation in Turkey: Epidemiologic Registry reported 37% effective INR in patients with nonvalvular AF (14) and 36.1% effective INR in those with valvular AF, including MHV (15). In the present study, we found that 43.6% of all patients (43.2% in AF, 44.2% in MHV) had INR within the therapeutic range, which is slightly better.

Warfarin-aspirin combination in atrial fibrillation

The European Society of Cardiology (ESC) guidelines for the management of patients with AF recommend OAC monotherapy

in patients with stable vascular disease (e.g., with no acute ischemic events or PCI in the preceding year) and remind that the addition of aspirin to OAC does not reduce the risk of stroke or vascular events (including myocardial infarction) but substantially increases bleeding events (9). The American Heart Association/American College of Cardiology (AHA/ACC) guidelines for the management of patients with AF have no recommendations about antiplatelets combined with OACs, except for patients undergoing revascularization procedures (10).

In this study, we observed that 14.6% of patients with AF without known arterial disease and 36.6% of patients with diabetes were receiving concomitant aspirin therapy, which suggests the intention of primary prevention. For patients with known arterial disease, concomitant aspirin use increased to 38.8%. In addition, we found that the warfarin-aspirin combination did not differ between thromboembolic risk categories determined by the CHADS-VASc score. Further, the proportion of combination therapy did not decrease but instead increased with increasing bleeding risk, calculated according to the HAS-BLED score. Remarkably, 30% of patients with a history of minor bleeding and 40% of patients with a history of major bleeding continued to use the warfarin-aspirin combination. These results suggest that risk scores are not used extensively and the decision to combine aspirin with anticoagulant therapy is largely driven by the prevention of cardiovascular events.

The rate of concurrent aspirin therapy in large, randomized trials of newer oral anticoagulants is remarkable. In the ARISTOTLE trial, concomitant aspirin use, which was left to the treating physician, was 24% (16). A combination with aspirin increased major bleeding from 2.78% in monotherapy to 3.92% in combination therapy in warfarin arm. Approximately 25% of patients with AF with concomitant arterial disease were taking aspirin, and approximately 15% of patients with AF without concomitant arterial disease were taking aspirin throughout the study period, as observed in our analysis. During the ROCKET-AF trial, in which 18% had a history of myocardial infarction, 36.2% of all patients on warfarin were taking aspirin concurrently (17). Finally, concomitant aspirin use was observed in approximately 20% of participants of the RE-LY study, in which a history of myocardial infarction was present in 17% of all participants (18).

Observational studies and randomized trials have demonstrated high rates of bleeding with the combination of aspirin and OAC (2,3,15). A meta-analysis of randomized controlled trials (1) comparing two treatment strategies showed that there was no difference in the risk for arterial thromboembolism with combination treatment in patients with atrial fibrillation (OR, 0.99; 95% CI, 0.47–2.07). There was no difference in all-cause mortality either (OR, 0.98; 95% CI, 0.77–1.25). Although the risk for major bleeding was higher in patients receiving warfarin-aspirin combination therapy than in those receiving warfarin therapy alone (OR, 1.43; 95% CI, 1.00-2.02).

The problem in antithrombotic management of patients with AF is 2-fold. On one hand, a considerable proportion of patients with embolic risk factors do not receive OAC therapy (13, 19), and on the other side, there is the problem of inappropriate combination of aspirin with warfarin, which ranges from 15% to 40% in the published literature (2,3,13,15-17), whereas it was 21.1% in our study. Perhaps more importantly, this practice occurs in patients with AF in the absence of firm evidence for clinical benefit. Additionally, there is no scientific proof that the warfarin-aspirin combination has beneficial effects in primary or secondary prevention of cardiovascular disease in patients with AF. Besides, published data support the use of OAC for secondary prevention in patients with CAD, and OAC is as effective as aspirin (4).

Warfarin-aspirin combination in mechanical heart valve replacement

There is a divergence of opinion in recent guidelines concerning antithrombotic therapy of patients with MHV. The ESC guidelines for the management of valvular heart disease (6) recommend the addition of low-dose aspirin to warfarin in patients with a mechanical prosthesis and concomitant atherosclerotic disease (Class IIa). These guidelines also stress that warfarin plus aspirin should not be prescribed to all patients with prosthetic valves. On the other hand, the ACC/AHA guidelines for the management of patients with valvular heart disease (7) recommend the addition of low-dose aspirin to anticoagulants in patients with MHV (Class I). Clinical Practice Guidelines for Antithrombotic and Thrombolytic Therapy for Valvular Disease of American College of Chest Physicians (8) suggest the addition of low-dose aspirin in patients with MHV with low bleeding risk (Grade 1B). However, they have cautioned about the use of combination therapy in patients with increased bleeding risk, such as a history of gastrointestinal bleeding. An updated recent meta-analysis (20) suggested a significant reduction in mortality (RR, 0.57; 95% CI, 0.42-0.78) and thromboembolic outcomes (RR, 0.43; 95% CI, 0.32-0.59) after the addition of antiplatelets with an increased risk of major hemorrhage (RR, 1.58; 95% CI, 1.14-2.18). On the basis of scientific evidence, it can be suggested that the two groups of patients with MHV do require long-term combination therapy, provided there is no increased bleeding risk. These are patients with known arterial disease and patients who experienced thromboembolic events under optimal anticoagulation.

In the present study, of all the patients with MHV, 32.7% were on warfarin-aspirin combination therapy. A recent prospective study of patients with MHV reported a much lower incidence (2.2%) of concomitant antiplatelet therapy (21). CAD and total vascular disease comprised 11.6% and 15.6% of patients with MHV, respectively, in the present study. We observed that 47.8% of patients with known vascular disease were receiving warfarin-aspirin combination. Similarly, 46.7% of patients with MHV with a history of CVA were receiving combination therapy, although it was uncertain whether CVA occurred under optimal anticoagulation. Patients with MHV plus AF can also be considered to have a higher thromboembolic risk. These patients were receiving aspirin more frequently than others in our study. On

the contrary, the decision to add aspirin was not affected by the bleeding risk of the patients, as calculated according to the HAS-BLED score, and 37.5% of patients with a history of major bleeding were found to take concurrent aspirin.

In summary, although patients with known arterial disease or AF were considered, the current practice of antithrombotic therapy in patients with MHV was a long way from the recommendations, and in general, bleeding risk (or history) was ignored in our study population.

Study limitations

The single-center nature of our study is a limiting factor. However, it should be noted that most patients are not followed by a single clinician (or hospital). For example, 10% (n=36) of all patients in this study had no previous record and additional 4.2% (n=15) had no regular follow-up at our institution. Convenient access to health services plays a major role in long-term follow-up of warfarin therapy. Besides, warfarin is a long-lasting therapy, and patients who have changed residency or traveled to different regions will visit different hospitals and clinicians with different prescription habits alike. Ultimately, the use of combination therapy or the achievement of treatment goals is affected by the diverse applications of warfarin therapy among practicing cardiologists. Therefore, we believe that results should be more or less comparable between different centers. Another limitation of this study was the inclusion of patients taking warfarin from a cardiology clinic. Data on AF and MHV could have been expanded with patients from neurology and cardiovascular surgery clinics, respectively. A large multidisciplinary registry of all patients taking OACs can be very informative. Finally, because the HAS-BLED score was calculated at one outpatient visit, the presence of labile INR and abnormal liver/kidney function may have been missed, so the total score may have been underestimated. Nevertheless, this does not change the fact that combination therapy was not used infrequently in patients with high bleeding risk.

Conclusion

Although there is no doubt that every patient must be evaluated individually, the warfarin-aspirin combination appeared to be significantly overused in patients with AF, main purpose being the prevention of cardiovascular events, and underused in patients with MHV, especially in patients with known arterial disease. In addition, risk score-based (e.g., CHADS-VASc and HAS-BLED) treatment decisions unfortunately did not take place in daily practice. Clinicians should be aware of additional antiplatelet therapy in patients using OACs. The need for combined anticoagulant-antiplatelet therapy should be questioned (or considered) in patients under OAC therapy based on individual thromboembolic and bleeding risks.

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