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Aspirin resistance among patients with new and recurrent ischemic heart disease episodes in Qassim region, Saudi Arabia

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Abstract. – OBJECTIVE: Aspirin resistance is described as the failure of aspirin to decrease the production of thromboxane A2 by platelets, which is the mechanism by which aspirin decreases platelet activation and aggregation. This study was performed to assess the prevalence of aspirin resistance among cardiovascular patients in al-Qassim, Saudi Arabia.

PATIENTS AND METHODS: The study used a survey of patients with first and recurrent attacks of ischemic heart disease (IHD) and available data from blood samples processed using a VerifyNow® kit, which measures aspirin reaction units (ARUs).

RESULTS: A total of 119 patients were included: 45 with their first IHD episodes and 74 with recurrent episodes. Of the surveyed patients, 40% with a first episode were younger than 50 years old, and 75.6% of them have been diagnosed with IHD during the previous 5 years. Of the patients with recurrent attacks, 45.9% were older than 60 years, and 54.1% of them have been diagnosed more than 5 years before. The group with first episodes of IHD had 133.2 ARUs, whereas the group with recurrent episodes had 168.5 ARUs (p=0.105). In the recurrent-episode group, 77% had diabetes; in the first-episode group, only 37.8% had diabetes (p≤0.001). Overall, 46.2% were overweight, 54.6% were nonsmokers, and 82.4% underwent percutaneous coronary intervention.

CONCLUSIONS: The study participants in both the new and recurrent IHD groups showed no sign of aspirin resistance. The presence of cardiovascular risk factors increased the likelihood of episode recurrence.

Key Words:
Anticoagulants, Antiplatelet resistance, Aspirin resistance, Clopidogrel, Cardiovascular disease.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide[1]. In 2015, Roth et al[2] reported 422.7 million cases of CVD and 17.92 million CVD-related deaths. In Saudi Arabia, a study performed by Al-Nozha et al[3] reported an estimated overall CAD prevalence of 5.5%.

Antiplatelet therapy is the mainstay of treatment for coronary artery disease (CAD), peripheral arterial disease, and ischemic cerebrovascular disease, and its benefits have been documented and established in several studies[4]. Currently, the drugs of choice for the prevention and treatment of thrombosis and CAD are antiplatelet drugs that target cyclooxygenase-1 (COX-1) (e.g., acetylsalicylic acid, or aspirin) or the platelet P2Y12 receptor (e.g., clopidogrel, prasugrel, or ticagrelor)[5]. The increasing number of CAD cases has meant that several organizations are giving more attention to these diseases. In 2016, the American College of Cardiology and the American Heart Association recommended dual antiplatelet therapy with aspirin and clopidogrel for patients with CAD[6]. Aspirin works by irreversibly inhibiting platelet COX-1 to impair the development of platelet-mediated atherothromboembolic events[7].

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Clopidogrel inhibits thrombosis by inhibiting ADP-induced platelet aggregation and by inhibiting collagen- and thrombin-induced platelet aggregation, increasing the concentrations of these agonists and preventing the negative effects of their aggregation[8].

In recent years, aspirin resistance has garnered attention and has become an important clinical issue[9]. An exact, universally accepted definition of aspirin resistance does not yet exist, as the majority of mechanisms involved in the failure of aspirin to prevent atherothromboembolic events do not fit the classic model of drug resistance. Specifically, the pharmacological target, COX-1, often remains sensitive to aspirin, but the ability of aspirin to suppress the systemic levels of thromboxane A2 (TXA2) and platelet reactivity may be attenuated by a wide range of other factors[7]. In 2009, the European Society of Cardiology studied the variability among individuals in terms of their responses to oral antiplatelet therapy; in that study, aspirin resistance was categorized as clinical resistance and laboratory resistance[10]. Regardless of the reasons for resistance, the prognostic impact of resistance has been shown in many studies. In 2003, a study performed by Grundman et al[11] showed that aspirin resistance was identified in 34% of patients with recurrent episodes of ischemic heart disease (IHD) who adhered to aspirin treatment for more than 5 years. Previous studies[12,13] have shown that patient noncompliance is the most common cause of a lack of response to the antiplatelet regimen.

Clinical resistance is defined as the occurrence of cardiovascular events during treatment with aspirin, whereas laboratory resistance is defined as the insufficient suppression of platelet activity, as evidenced by *in vitro* assays, despite the current use of aspirin. It has been previously discussed the mechanism underlying aspirin resistance. Multiple factors may affect the inhibition of TXA2 production/activation by aspirin and interfere with platelet aggregation, thereby causing laboratory aspirin resistance. Many factors lead to clinical aspirin resistance[14]. A Swedish study[15] showed that more than 40% of patients using antiplatelet medications are not optimally adherent or are complexly nonadherent to treatment. Nonadherence was associated with a low education level, female sex, a history of depression, a history of diabetes mellitus, and cigarette smoking. Adverse events were noted as the cause of cessation of low-dose ASA treatment in nearly 50% of patients[15]. Resistant to antiplatelet therapy is not limited to aspirin. In a prospective study that evaluated the antiplatelet effect of clopidogrel, approximately 25% of patients who underwent percutaneous coronary intervention (PCI) after ST-elevation myocardial infarction (i.e., STEMI) with stenting were resistant to clopidogrel and were therefore at increased risk for recurrent thrombosis[16].

Laboratory aspirin resistance is defined as the failure of therapeutic doses of aspirin to inhibit platelet aggregation, and the definition is based on the direct measurement of platelet function or the detection of a lack of reduction in the expression of TXA2[17]. The ineffectiveness of clopidogrel at inhibiting platelet aggregation, as measured in the laboratory, is known as clopidogrel resistance[18]. Many factors, such as clinical conditions[19], drug interactions[20,21], and genetic variations[22], affect the development of clopidogrel resistance.

One hundred ninety patients with a history of myocardial infarction (MI) were evaluated by Schwartz et al[23] in 2005 using an arachidonic acid-stimulated light aggregometry test at three different time points: while taking their usual daily dose of aspirin, 1 week after discontinuing aspirin treatment, and 2 hours after the supervised administration of aspirin. At the first time point, 17 patients (9%) showed no aspirin inhibition of platelet aggregation; 2 hours after the observed aspirin administration, all but one patient exhibited scant observed aspirin inhibition.

This study was performed to identify the prevalence and causes of antiplatelet treatment resistance in the al-Qassim region of Saudi Arabia.

Patients and Methods

Participant Selection

We recruited patients from February to September 2018 after their admission to King Fahad Specialist Hospital, Prince Sultan Cardiac Centre, Buraidah, al-Qassim, Saudi Arabia. We collected a total of 119 responses from patients who provided their informed consent and divided the participants into two groups: those with a first heart attack (n=45) and those with recurrent heart attacks (n=74).

Inclusion Criteria

We included male and female patients with a first or a recurrent episode of IHD who were

receiving 81 mg of aspirin alone, combined with 75 mg of clopidogrel, or combined with 90 mg of ticagrelor.

Exclusion Criteria

Patients taking oral anticoagulants and those with recurrent IHD episodes who had experienced their first IHD episode within the previous month were excluded. Ethical approval for the study was obtained from the subcommittee of Health Research Ethics in Qassim University, Buraidah, Saudi Arabia.

Clinical Resistance

We assessed clinical resistance using a structured survey that was developed on the basis of an extensive literature review. The questionnaires, which were originally written in English, were translated into Arabic. The survey included demographic data, educational level, smoking status, family history, history of IHD, history of drug therapy, and adherence.

Laboratory Resistance

The platelet response to aspirin was measured using the VerifyNow® aspirin reaction units (ARU) test, which measures arachidonic acid-induced platelet aggregation. A result of <550 ARUs is evidence of platelet inhibition by aspirin. A result of ≥550 ARUs indicates no evidence of aspirin-induced platelet inhibition. A registered nurse drew 2 mL of blood from each patient into a tube containing 3.2% sodium citrate after obtaining informed consent. Any samples with signs of clotting were excluded.

Statistical Analysis

All categorical variables are presented as the counts and proportions (%); continuous variables are summarized as the means ± standard deviations. The relationships between antiplatelet therapy and recurrent episodes of IHD among patients stratified by baseline characteristics and comorbid diseases were assessed with Fischer's exact test, and the comparisons between anthropometric measures and laboratory results between patients with recurrent or first episodes of IHD were conducted using the Mann-Whitney U test (nonparametric test). The Shapiro-Wilk test was used to assess the normality of the distribution of data. A p-value of 0.05 indicated statistical significance. All statistical data were analyzed using the Statistical Package for Social Sciences, version 21 (SPSS Inc., Armonk, NY, USA).

Results

We analyzed 119 patients who were admitted due to IHD episodes. Table I presents the baseline characteristics of the 119 patients. The ages ranged from 18 to 81 years (mean 57.8 years), and the most common age group was patients older than 60 years (39.5%). Male patients predominated (85.7% *vs.* 14.3% female patients), and educational levels were almost equally distributed across the cohort (uneducated: 21.8%, elementary education: 21%, intermediate education: 21.8%, secondary education: 16%, higher education: 19.3%).

Table II shows the platelet activity, measured in ARUs, of patients with first and recurrent episodes of IHD. The mean platelet count was higher in those with a recurrent IHD episode (168.5±83.4) than in those with a first episode (133.2±77.7). However, the difference was not significant (p=0.105) according to the Mann-Whitney U test (Figure 1).

Table III depicts the adherence to drug therapy among patients with first and recurrent IHD episodes. In patients who were not adherent to aspirin therapy, the most frequently mentioned reason for nonadherence was "it was not important" (67.7%) followed by "failure to remember" (19.4%) and "side effects" (12.9%). Of those who were not adherent to clopidogrel, approximately 58.8% said "it was not important", 35.3% failed to remember to take it, and only one patient (0.80%) did not adhere because of side effects. In addition, 16 patients responded about their adherence to ticagrelor; among them, 13 patients were adherent, and 3 patients were not, mainly because of side effects (n=2) or failure to remember (n=1). Finally, nearly all the patients (96.6%) were taking other types of medications, and the most common were statins (98.2%). When comparing patients who had a first IHD episode with those who had recurrent IHD episodes, adherence to clopidogrel (p=0.023) and taking clopidogrel as the brand product Clogrel (Aja Pharma, Hail city, Hail region, Saudi Arabia) (p<0.001) were significantly associated with the first episode, whereas taking aspirin for longer than 1 year (p=0.045), taking clopidogrel as the brand product Plavix (Sanofi Winthrop, France) (p=0.001), and taking proton pump inhibitors (PPIs) (p=0.029) were

Table I. Baseline characteristics of patients.

Study variables	Overall N (%) (n = 119)	First episode N (%) (n = 45)	Recurrent episode N (%) (n = 74)	*p*-value*
Age group				
• < 50 years	31 (26.1%)	18 (40.0%)	13 (17.6%)	**0.023****
• 51-60 years	41 (34.5%)	14 (31.1%)	27 (36.5%)	
• > 60 years	47 (39.5%)	13 (28.9%)	34 (45.9%)	
Sex				
• Male	102 (85.7%)	40 (88.9%)	62 (83.8%)	0.591
BMI level				
• Normal (18.5-24.9)	12 (10.1%)	03 (06.7%)	09 (12.2%)	0.162
• Overweight (25.0-29.9)	55 (46.2%)	17 (37.8%)	38 (51.4%)	
• Obese (30-34.9)	35 (29.4%)	19 (42.2%)	16 (21.6%)	
• Severely obese (35-39.9)	09 (07.6%)	04 (08.9%)	05 (06.8%)	
• Morbidly obese (40 or higher)	08 (06.7%)	02 (04.4%)	06 (08.1%)	
Smoking status				
• Smoker	25 (21.0%)	06 (13.3%)	19 (25.7%)	0.297
• Non-smoker	65 (54.6%)	27 (60.0%)	38 (51.4%)	
• Ex-smoker	29 (24.4%)	12 (26.7%)	17 (23.0%)	
If smoker, number of cigarettes/day†				
• ≤ 20	15 (60.0%)	03 (50.0%)	12 (63.2%)	0.653
• > 20	10 (40.0%)	03 (50.0%)	07 (36.8%)	
Type of intervention				
• None	05 (04.2%)	02 (04.4%)	03 (04.1%)	0.272
• PCI	98 (82.4%)	38 (84.4%)	60 (81.1%)	
• CABG	14 (11.8%)	03 (06.7%)	11 (14.9%)	
• Fibrinolysis	01 (0.80%)	01 (02.2%)	0	
• PTCA	01 (0.80%)	01 (02.2%)	0	
Time since diagnosis of IHD				
• ≤ 5 years	68 (57.1%)	34 (75.6%)	34 (45.9%)	**0.002****
• > 5 years	51 (42.9%)	11 (24.4%)	40 (54.1%)	
Anthropometric measures				
• Weight in kg (mean ± SD)	82.6 ± 14.1	84.2 ± 13.7	81.7 ± 14.3	0.339**
• Height in cm (mean ± SD)	165.4 ± 7.68	165.8 ± 7.71	165.1 ± 7.69	0.727**

Notes: †Non-smokers and ex-smokers were excluded from the analysis. **p*-value was calculated with Fisher's exact test. ** p-value was calculated with the Mann-Whitney U test. ***Significant at $p < 0.05$. *Abbreviations:* BMI: Body Mass Index; CABG, Coronary artery bypass; PCI, Percutaneous coronary intervention; grafting; PTCA, Percutaneous transluminal coronary angioplasty.

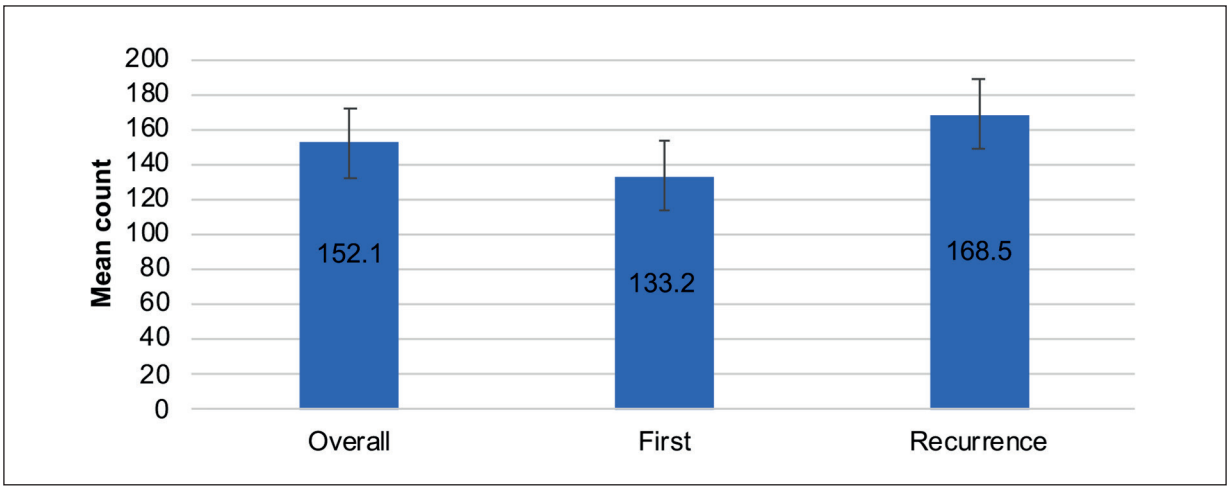

Figure 1. Mean platelet counts in patients with first and recurrent episodes of IHD.

Table II. Platelet activity in patients with first and recurrent IHD episodes (n=43).

Values shown are the means ± SDs				
Parameter	**Overall**	**First episode**	**Recurrent episode**	***p*-value***
ARU	152.1 ± 81.8	133.2 ± 77.7	168.5 ± 83.4	0.105

Notes: **p*-value was calculated with the Mann-Whitney U test. *Abbreviations:* ARU, Aspirin Resistant Unit.

significantly associated with recurrent episodes.

Table IV shows the comorbid diseases in patients with first and recurrent IHD episodes. One-third of patients (33.6%) had a family history of IHD. We also observed that 78.4% of diabetic patients were diagnosed more than 5 years before. In addition, 12.6% had peptic ulcers, and 89.1% reported no history of blood disorder. We found that diabetes ($p<0.001$) and hypertension ($p=0.002$) were significantly associated with recurrent IHD episodes.

Table V shows the characteristics of patients with recurrent IHD episodes. The most common intervention for recurrent episodes was PCI (74.3%), and the most common interval between episodes was longer than 6 months (78%). With regard to the metabolic parameters in patients with recurrent episodes, the mean cholesterol, prothrombin time (PT), activated partial thromboplastin time (APTT), fasting blood glucose (FBG), and hemoglobin A1c (HbA1c) were 3.9 mmol/L, 12.5 sec, 31.4 sec, 11.2 mmol/L, and

Table III. Adherence to drug therapy among patients with first and recurrent IHD episodes N (%).

Parameters	**Overall (n = 119)**	**First episode (n = 45)**	**Recurrent episode (n = 74)**	***p*-value***
Drug therapy				
• Aspirin only	14 (11.8%)	04 (08.9%)	10 (13.5%)	0.371
• Aspirin and clopidogrel	90 (75.6%)	33 (73.3%)	57 (77.0%)	
• Aspirin and ticagrelor	15 (12.6%)	08 (17.8%)	07 (09.5%)	
Adherence to aspirin therapy (n=115)				
• Yes	84 (73.0%)	33 (75.0%)	51 (71.8%)	0.830
• No	31 (27.0%)	11 (25.0%)	20 (28.2%)	
Duration of aspirin therapy (n=105)				
• ≤ 1 year	10 (09.5%)	07 (17.1%)	03 (04.7%)	**0.045****
• > 1 year	95 (90.5%)	34 (82.9%)	61 (95.3%)	
Adherence to clopidogrel therapy (n=85)				
• Yes	68 (80.0%)	29 (93.5%)	39 (72.2%)	**0.023****
• No	17 (20.0%)	02 (06.5%)	15 (27.8%)	
Duration of clopidogrel therapy				
• ≤ 1 year	18 (23.1%)	07 (23.3%)	11 (22.9%)	1.000
• > 1 year	60 (76.9%)	23 (76.7%)	37 (77.1%)	
Brand name of clopidogrel used† (n=59)				
• Plavix	36 (61.0%)	05 (27.8%)	31 (75.6%)	**0.001****
• Pedovex	19 (32.2%)	09 (50.0%)	10 (24.4%)	0.072
• Clogrel	29 (49.2%)	17 (94.4%)	12 (29.3%)	**< 0.001****
Adherence to ticagrelor therapy (n=16)				
• Yes	13 (81.3%)	06 (66.7%)	07 (100%)	0.213
• No	03 (18.8%)	03 (33.3%)	0	
Duration of ticagrelor therapy (n=15)				
• ≤ 1 year	03 (20.0%)	01 (11.1%)	02 (33.3%)	0.525
• > 1 year	12 (80.0%)	08 (88.9%)	04 (66.7%)	
Type of other medication†, (n=115)				
• PPI	70 (61.4%)	21 (47.7%)	49 (70.0%)	0.029**

Notes: †Variable with multiple responses. **p*-value was calculated with Fisher's exact test. **Significant at $p < 0.05$. *Abbreviations:* PPI, Proton-Pump Inhibitor.

Table IV. Comorbid diseases in patients with first and recurrent episodes of IHD.

Study variables	Overall N (%) (n = 119)	First episode N (%) (n = 45)	Recurrent episode N (%) (n = 74)	*p*-value*
Diabetes				
• Yes	74 (62.2%)	17 (37.8%)	57 (77.0%)	**< 0.001****
• No	45 (37.8%)	28 (62.2%)	17 (23.0%)	
When was DM diagnosed? (n=74)				
• < 1 year	02 (02.7%)	0	02 (03.5%)	0.403
• 1-5 years	14 (18.9%)	05 (29.4%)	09 (15.8%)	
• > 5 years	58 (78.4%)	12 (70.6%)	46 (80.7%)	
Hypertension				
• Yes	67 (56.3%)	17 (37.8%)	50 (67.6%)	**0.002****
• No	52 (43.7%)	28 (62.2%)	24 (32.4%)	
When was HTN diagnosed? (n=67)				
• < 1 year	10 (14.9%)	03 (17.6%)	07 (14.0%)	0.706
• 1-5 years	57 (85.1%)	14 (82.4%)	43 (86.0%)	
If non-hypertensive, taking antihypertensive medications (n=52)				
• Yes	37 (71.2%)	21 (75.0%)	16 (66.7%)	0.553
• No	15 (28.8%)	07 (25.0%)	08 (33.3%)	
Dyslipidemia				
• Yes	36 (30.3%)	12 (26.7%)	24 (32.4%)	0.544
• No	83 (69.7%)	33 (73.3%)	50 (67.6%)	
When was dyslipidemia diagnosed? (n=36)				
• < 1 year	02 (05.6%)	02 (16.7%)	0	0.200
• 1-5 years	17 (47.2%)	05 (41.7%)	12 (50.0%)	
• > 5 years	17 (47.2%)	05 (41.7%)	12 (50.0%)	
If without dyslipidemia, taking anti-dyslipidemia medication (n=83)				
• Yes	71 (85.5%)	28 (84.8%)	43 (86.0%)	1.000
• No	12 (14.5%)	05 (15.2%)	07 (14.0%)	
Peptic ulcer				
• Yes	15 (12.6%)	05 (11.1%)	10 (13.5%)	0.783
• No	104 (87.4%)	40 (88.9%)	64 (86.5%)	

Notes: **p*-value was calculated using Fisher's exact test. **Significant at $p < 0.05$. *Abbreviations:* IHD, ischemic heart disease; HTN, Hypertension.

7.70%, respectively. For detailed information, see the **Supplementary Tables I-III**.

Discussion

In recent years, identifying the pattern of response to antiplatelet therapy in patients with CAD has become crucial. A proportion of patients experiences recurrent cardiac events despite an established antiplatelet treatment regimen. This study investigated the prevalence of antiplatelet treatment resistance among patients with first and recurrent IHD episodes and identified the reasons for that resistance.

Ageing affects the vasculature, leading to increased arterial thickening and stiffness and to endothelial dysfunction. These changes subsequently lead to increased systolic pressure, which is a risk factor for the development of atherosclerosis[24]. Our study showed a significant relationship between age group and the type of episode, as most patients with first episodes were younger than those with recurrent episodes. Precisely 40% of the patients with first episodes were younger than 50 years old, and only 17.6% of the patients in this age group had a recurrent episode. A total of 45.9% of the patients who were older than 60 years had recurrent episodes, whereas 28.9% had a first episode. A registry study[25] performed in 2014 in Sweden and the United Kingdom showed mean ages of 71.2 and 69.5 years for patients with acute myocardial infarction, respectively.

There is abundant evidence supporting sex-specific risks of CVD, but the biological bases for these differences remain unknown[26]. Most

Table V. Characteristics of patients with recurrent IHD episodes (n=74).

Characteristic	N (%)
Type of intervention	
• None	11 (14.9%)
• PCI	55 (74.3%)
• CABG	03 (04.1%)
• Fibrinolytic	05 (06.8%)
Interval since previous episode (n=41)	
• ≤ 1 month	08 (14.9%)
• 1-3 months	0
• > 3 months-6 months	01 (0.80%)
• > 6 months	32 (78.0%)
Metabolic parameters	**Mean ± SD**
• Cholesterol (mmol/L)(n=24)	03.9 ± 1.51
• PT (sec) (n=28)	12.5 ± 1.73
• APTT (sec) (n=49)	31.4 ± 4.62
• FBG (mmol/L) (n=9)	11.2 ± 6.48
• HbA1c (%) (n=11)	7.70 ± 1.93

Abbreviations: PCI, Percutaneous coronary intervention; CABG , Coronary artery bypass grafting; PT , Prothrompine time; APTT, activated partial thromboplastin time ; FBG , Fasting blood glucose; HbA1c , hemoglobin A1c.

patients in this study were men (85.7%), which could be attributed to the demographics in the study region. According to the 2018 census of the al-Qassim region, 1.9% of the men and 1.2% of the women had CVD[27]. In contrast, Cha et al[28] in 2016 reported more female than male patients among both those with first episodes and those with recurrent episodes.

The body mass index (BMI) of the study participants was high overall and differed between the two groups. Most patients with a first episode were obese (42.2%), whereas most patients with recurrent episodes were severely overweight (51.4%). This difference could be attributed to the educational and medical efforts regarding body weight and diet made by the Ministry of Health after the first episode. However, a cohort study[28] in 2016 showed no difference in BMI between patients with and without recurrent episodes.

Most patients with recurrent episodes underwent PCI as an intervention (74.3%). A 2012 study[29], in which 85.3% of patients with recurrent infarctions underwent emergency PCI, was similar to ours.

Smoking is a risk factor for several cardiac diseases. The majority of patients with first and recurrent episodes were nonsmokers (60% and 51.4%, respectively). Smokers reported smoking fewer than 20 cigarettes per day. Similar results were reported in 2013 by Kim et al[30], who studied the effect of smoking on several diseases and found that current smokers had a higher rate of CVD than did those who had quit smoking.

The Verify Now ARU test is an initial way in emergencies to identify patients who are taking aspirin, which helps avoiding the risk of bleeding during major surgery[31]. In this study, the measured ARUs did not differ between the two groups, and both groups had values within the normal range. According to the test manual, a value less than 550 ARUs represents no aspirin resistance. The group with first episodes had a mean value of 133.2 ARUs, and the group with recurrent episodes had a value of 168.5 ARUs; thus, the platelets in both groups still responded to aspirin. The lack of a significant difference could be attributed to the atypical distribution of the data. The Saudi Food and Drug Administration announced in January 2019 the withdrawal of the aspirin product Jusprin (Julphar, United Arab Emirates), a brand of aspirin produced in the United Arab Emirates, because of quality issues – specifically those pertaining to its stability. Jusprin was the brand provided to the patients by the Ministry of Health. Use of this product could be a reason for the recurrent episodes, even among those who adhered to aspirin treatment. A study[32] in 2016 measured the ARUs in aspirin-resistant and nonresistant patients. The resistant group had a value of 610 ARUs, which was higher than the cut-off, but the nonresistant group had a lower value (442).

Despite the availability of other options, most of the patients in our study were receiving regimens using aspirin and clopidogrel. In the PLATO study, treatment with ticagrelor was associated with fewer total events, including first and recurrent cardiovascular events, than clopidogrel[33].

The patients in our study were not completely adherent to their medication regimens. Approximately, 73% adhered to aspirin treatment, 80% adhered to clopidogrel treatment, and 81.3% adhered to ticagrelor treatment. Their main reason for nonadherence to aspirin and clopidogrel was that patients considered their antiplatelet medications unimportant (67.7% for aspirin and 58.8% for clopidogrel); 66% of the patients who were nonadherent to ticagrelor cited side effects as a reason. A 2019 study[34] in Vietnam showed similar results among patients with MI: approximately 70% reported adherence, and nonadherence was attributed primarily to financial reasons.

In terms of duration, most patients have been treated with antiplatelets for longer than 1 year.

However, a systematic review and meta-analysis[35] in 2015 showed that an extended duration of dual antiplatelet therapy (>6 months) did not yield any benefits with regard to the risk of all-cause, cardiovascular, or noncardiovascular mortality compared with aspirin alone or a short duration of dual antiplatelet therapy. In addition, the 2016 ACC/AHA guidelines[6] did not report any benefit of or make recommendations for more than 1 year of dual antiplatelet therapy.

The specific brand name products used by patients in this study varied substantially between the groups with first and recurrent episodes. Most patients with first episodes were receiving clopidogrel as Clogrel (Aja Pharma, Hail city, Hail region, Saudi Arabia), whereas the patients in the recurrent-episode group were receiving the same drug as Plavix (Sanofi Winthrop, France). This difference could have occurred because the Ministry of Health used to provide Plavix but now provides Clogrel.

Most patients were receiving treatments other than antiplatelet medications: more than 90% of patients reported taking other medications. Statins were the most common, followed by PPIs, and then, nonsteroidal anti-inflammatory drugs (which were reported by only a few patients). Statins have many benefits: they improve endothelial function, modulate inflammatory responses, maintain plaque stability, and prevent thrombus formation[36]. High-intensity statins are recommended as part of the treatment plan for CVD[37]. PPIs should be used in patients with a history of prior gastrointestinal bleeding who require dual antiplatelet therapy, as per the 2011 PCI guidelines[6]. According to a 2011 study, 37.3% of patients with CHD in the Middle East were treated with statins[38].

The World Heart Federation has listed several risk factors for CVD. Modifiable risk factors include physical inactivity, hypertension, diabetes mellitus, smoking, diet, and obesity; nonmodifiable risk factors include family history, age, and sex[39]. In our study, most patients in both groups reported a family history of IHD. In the United States, according to the 2011 heart disease and Stroke Statistics, 13.3% of adults aged 20 years or older reported having a parent or sibling with a heart attack or angina before age 50 years[40]. Moreover, a relevant parental history increases the odds of MI up to six times compared with a control group[41].

Blood pressure has strong associations with MI and several cardiac diseases[42]. Diabetes and hypertension were more prevalent among patients with recurrent episodes than among those with first episodes, although most participants did not have diabetes or hypertension. In a 2017 study[43], 82.5% of patients with MI also had hypertension, whereas only 46.6% of them had diabetes. Another study[25] based on registries of patients with acute MI in Sweden and the United Kingdom recorded that 47.3% of patients in the United Kingdom had a history of hypertension and 17.6% had a history of diabetes, whereas 45.2% of patients in Sweden had a history of hypertension and 22.7% had a history of diabetes.

Hyperlipidemia is an important risk factor for CVD and can be characterized by high cholesterol, high triglycerides, or both[44]. Dyslipidemia was not common in either group in our study. However, in patients with recurrent episodes, most reported taking antidyslipidemia medications despite no diagnosis of dyslipidemia. This treatment could have resulted from recommendations in the guidelines for the use of high-dose statins after STEMI[37]. In contrast, 68% of the patients in a study by Hess et al[43] who had a first cardiovascular event, also experienced hyperlipidemia. The study by Stone et al[44] evaluated the baseline characteristics of the patients who had reinfarction after STEMI and those who did not. They reported that 48.4% of the reinfarction group had hyperlipidemia and 42.1% of STEMI group without reinfarction had hyperlipidemia. They found a median time to first reinfarction of 244 days; similarly, most patients in our study had recurrent episodes more than 6 months after the previous infarction.

Some metabolic parameters were abnormal in the group with recurrent episodes of IHD. The mean cholesterol level was lower than normal, which could be attributed to the use of statins after the first episode. A study by Cha et al[28], which reported a slightly higher mean cholesterol value of 4.73 mmol/L, supports this premise. The blood glucose measurements (FBG and HbA1c) were abnormally high in patients in the recurrent-episode group; these increases could reflect the diabetic status of the majority of this group. Our results corroborate those in the 2016 study by Cha et al[28].

APTT is a coagulation screening test that assesses the status of patients with coagulation abnormalities. The PT measures the time required for clotting to occur after the addition of a source of tissue factor to recalcified, citrated plasma. Several medications (heparin, low-molec-

ular-weight heparin, and warfarin) will prolong the APTT and PT[45]. In our study, the coagulation parameters of PT and APTT in patients with recurrent episodes were normal. The range for the PT is 10-13 sec, and the range for the APTT is 22-37 sec[46].

One major limitation faced by this study was the low rate of enrollment by patients in the al-Qassim region. In addition, enrolled patients were not always forthright with the data collector during the first interview after their admission. Furthermore, these findings were predominantly from a male population and from patients with diabetes but without hyperlipidemia, so they cannot be more widely attributed to other patient populations.

Conclusions

No clear evidence of aspirin resistance was found in our participants, and other factors may have contributed to the recurrence of IHD episodes. The study showed a high level of compliance with antiplatelet medications. The presence of cardiovascular risk factors increased the likelihood of episode recurrence. Diabetes and hypertension tended to be associated with recurrent episodes. Other risk factors, such as family history, BMI, and smoking, were not associated with recurrent episodes.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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