MEDICAL SCIENCE

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DISCOVERY

SCIENTIFIC SOCIETY

Assessment of the extent, causes and prevalence of aspirin resistance among Saudi and Egyptian patients: A comparative study

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ABSTRACT

Background and Aim: Aspirin (antiplatelets) was significantly effective as anticoagulant in reducing cardiovascular disease (CVD) morbidity and mortality. Aspirin resistance was reported by some studies so; the aim of this study is to assess the aspirin resistance prevalence and the causes of this resistance in patients among Saudis and Egyptians. *Methods:* This study will be carried out among Saudi and Egyptians with previous strokes or thromboembolism and using aspirin as anticoagulant through interview containing some questions about the reasons for refusing aspirin, degree of satisfaction of aspirin as anticoagulant and the signs of aspirin un-efficacy. *Results:* There were 786 participants in total, the majority of them were women (414 were from the KSA and 372 were from Egypt). Aspirin use was common among both countries and the majority of them for their metabolic disorders. Only 7.0% & 9.9% of Saudis & Egyptians switched from aspirin to other anticoagulants due to aspirin inefficacy (1.2% & 1.1%) or bleeding (1.2% & 2.2%), or gastric ulcer (1.7% & 2.7%) or sensitivity (2.7% & 4.0%), respectively. Most participants were strongly in favor of using aspirin as an anticoagulant. *Conclusion:* We can conclude that low percentage of aspirin resistance was observed and Patients with an inadequate aspirin response have an increased likelihood for subsequent resistance. More research was needed to be done on more patients to confirm these results.

Keywords: Aspirin resistance & Prevalence, Strokes, Thromboembolism, Blood Coagulation.

1. INTRODUCTION

Aspirin is a non-steroidal anti-inflammatory drug that acts as irreversible

inhibitor of platelet prostaglandin synthase activity, widely used antiplatelet for secondary prevention, at low doses (Del-Giovane et al., 2021). It inhibits thromboxane (TX) A2 generation by addition of acetyl with a serine residue at locus 529 of the cyclooxygenase-1 (COX-1) enzyme (Funk et al., 1991). Anti-platelet drugs reduce the risk of myocardial infarction (MI), vascular death after an acute ischemic stroke (AIS), recurrent stroke and /or transient ischemic attack (TIA) (Niu et al., 2016).

A reduced dose of Aspirin (less than 150 mg) used as secondary prevention in cardiovascular diseases (CVD) and has been approved by the food and drug administration (FDA) (Alkhail et al., 2016). Aspirin was significantly effective in reduction of CVD morbidity and mortality or patients underwent CVD surgery. Despite of many clinical trials approved the efficacy of aspirin in reducing CV events, but others have contradictory results. In Addition, safety and efficacy of aspirin when used as primary preventive has some variation between randomized controlled trials (Mahmoud et al., 2019; Gul et al., 2023).

These differences makes the guidelines of American Heart Association/American College of Cardiology support the personalized intervention of aspirin as primary prevention agent based on patient's factors (Arnett et al., 2019). Also, Williams et al., (2015) and Al-Hazimi et al., (2020) suggested for high-risk patients by an agency, while this suggestion is not going with primary prevention for any risk level by the European Society of Cardiology (William et al., 2015; Aboelnaga et al., 2021). Bryant et al., (2006) and Frossard et al., (2004) found that aspirin resistance has been associated with adverse clinical events, increasing both morbidity and mortality.

In recent years, aspirin resistance has garnered attention and has become an important clinical issue (Pamukcu et al., 2005). Most of mechanisms which describe aspirin resistance does not suitable because of its resistance as the target, COX-1, remains subtle to aspirin, but its activity to inhibit the platelet reactivity may be affected by other factors (Floyd and Ferro, 2014; Premkumar et al., 2023).

In Asians, few studies about the popularity of aspirin consumption and most of them among diabetic patients. In certain patients, low dose aspirin therapy is not effective in preventing acute atherothrombotic complications and for this reason the term "aspirin resistance" was introduced (Floyd and Ferro, 2014). The beneficial effects of thienopyridines observed may be multifactorial. The aim of our study is to assess the aspirin resistance and its prevalence among Saudis and Egyptian patients.

2. METHODS

Study Design

This cross-sectional comparative study was done between patients using aspirin among Egyptians and Saudis. The aim of our study is to assess the aspirin resistance prevalence and causes in patients in Saudi Arabia and Egypt. Data was collected from patients who are suffering from strokes or thromboembolism and receiving aspirin through interview contain questions about their demographic and clinical characteristics, causes of using or refusing receiving aspirin, degree of satisfaction of aspirin as anticoagulant, degree of aspirin efficacy and the signs of aspirin un-efficacy.

All participants were well-informed about the nature of the study and informed them that the participation is voluntary. Another data was collected through an online questionnaire for all people to assess the prevalence of aspirin resistance. We illustrated at the start of the questionnaire or interview some phrases about the participation is not mandatory and they can stop participation at any time without any harm. Also, we said other sentence about data security which stated that all data of participants was secured, coded and kept in a locked file with the access to the researchers only.

This study has been go through and accepted by the research Ethical Committee at the University of Hail research number (H-2022-350). The total number of participants who completed the answers of the questionnaire and questions of the interview were 786 (414 from KSA and 372 from Egypt) and it was collected from October 2022 to February 2023.

Statistical analysis

It was done with Statistical Package for Social Sciences (version 25 SPSS Inc, Chicago, IL, USA). Categorical variables were presented using frequencies (n) and percentages (%). P-value ≤ 0.05 was considered statistically significant according to Pearson Chi-Square test.

Inclusion criteria

The participants were males or females with age of 20-years-old and above. Also, patients who were using aspirin as anticoagulant.

Exclusion criteria

People with age less than 20-years-old and any patients with mental disorders

3. RESULTS

This study disclosed that the total participants was 786, from Saudi Arabia (414) and from Egypt (372), the percentage of females was great either from Saudis (81.9%) or from Egyptians (88.4%). Most participants from ages between 20-50 years-old and their level of education starting from secondary school and above; from Saudis (80.8% & 83.3%) or from Egyptians (71.5% & 87.4%); respectively. Smokers were (12.3% & 11.0%) and playing sports (35.3% & 44.1%) from Saudis and Egyptian respectively (Table 1). Most of participants with normal Hb1AC, also the majority of participants without history of CVDs (more than 80%) or chronic diseases (more than 60%). There was a significant difference (P value <0.05) between Saudis and Egyptians in all parameters (Table 1).

Table 1 Demographic characteristics among Egyptian and Saudi population (Total n=786 Participants, n= 414 (Saudis), n=372 (Egyptians))

Question	Answer	Saudis n (%)	Egyptians n (%)	P- value
The age of participants (years)	20-35	181 (43.7)	170 (45.7)	0.011*
	36-50	195 (47.1)	96 (25.8)	
	51-65	34 (8.2)	76 (20.4)	
	>65	4 (1.0)	30 (8.1)	
Gender	Male	75 (18.1)	43 (11.6)	0.020*
	Female	338 (81.9)	329 (88.4)	
Level of education	Medium	69 (16.7)	47 (12.6)	0.010*
	Secondary and above	345 (83.3)	325 (87.4)	
Smoking	Yes	51 (12.3)	41 (11.0)	0.007*
	No	363 (87.7)	331 (89.0)	
Sports	Yes	146 (35.3)	164 (44.1)	0.008*
	No	268 (64.7)	208 (55.9)	
History of CVDs & CADs	Peripheral Artery Diseases	3 (0.7)	11 (3.0)	0.012*
	Myocardial infarction (MI)	10 (2.4)	12 (3.2)	
	TIA	12 (2.9)	13 (3.5)	
	IHD	29 (7.0)	25 (6.7)	
	DVT	13 (3.1)	11 (3.0)	
	Stroke	8 (1.9)	10 (2.9)	
	None	354 (85.5)	301 (80.9)	
History of Chronic Diseases	HTN	62 (15.0)	90 (24.2)	0.010*
	Rheumatoid Arthritis	11 (2.7)	20 (5.4)	
	Dyslipidemia	16 (3.9)	58 (15.6)	
	Diabetes	39 (9.4)	62 (16.7)	
	Arteriosclerosis	11 (2.7)	15 (4.0)	
	Obesity	83 (20.0)	54 (14.5)	
	CKD	12 (2.9)	10 (2.9)	
	None	303 (73.2)	234 (62.9)	
Hb 1AC (Diabetes DM)	Less than 7 (Normal)	334 (80.7)	287 (77.2)	0.009*
	Equal or more than 7 (High)	80 (19.3)	(22.8)	

*Significant difference at p value <0.05

Our results showed that the percentage of patients who were not received aspirin was 36.5% & 29.3%; so, the prevalence of using aspirin was 63.5% & 70.7%; from Saudis and Egyptians respectively. The daily dose used by participants was different according to their cases, 21.5% Vs. 31.5 (75mg), 24.6% Vs. 21.5% (85mg) and 17.4% Vs. 17.7% (100mg) and the duration of aspirin treatment was varied, one year or less (23.7% Vs. 36.3%), while more than one year (39.9% Vs. 34.4%) from Saudis & Egyptians respectively (Table 2).

About 53.1% vs. 64.5% were using aspirin as a protective from blood coagulation and 24.9% vs. 38.7% was adherent to treatment with aspirin from Saudis & Egyptians respectively. Other drugs were used by the participants with aspirin for treatment of different diseases as in (Table 2). Most of participants used aspirin as a protective from MI (24.6% vs. 36.3%), Brain stroke (13.8% vs. 16.7%), IHD (13.3% vs. 19.4%) while used for other diseases but with low percentages such as TIA, DVT, After Cardiac Surgery, Clots in Pulmonary artery & peripheral arteries, Stroke in coronary artery, but others used it as analgesic (21.5% vs. 19.4%) from Saudis & Egyptians respectively.

Table 2 Assessment of patients Knowledge about Aspirin among Egyptian and Saudi population (Total n=786 Participants, n= 414 (Saudis), n=372 (Egyptians))

Question	Answer	Saudis n (%)	Egyptians n (%)	P- value
Daily dose of Aspirin (mg)	75 mg	89 (21.5)	117 (31.5)	0.030*
	85 mg	102 (24.6)	80 (21.5)	
	100 mg or more	72 (17.4)	66 (17.7)	
	Don't receive Aspirin	151 (36.5)	109 (29.3)	
Duration of Aspirin Treatment	One year or less	98 (23.7)	135 (36.3)	0.021*
	More than one year	165 (39.9)	128 (34.4)	
	Don't receive Aspirin	151 (36.5)	109 (29.3)	
Adherence to Aspirin treatment	Yes	103 (24.9)	144 (38.7)	0.013*
	No	160 (38.6)	119 (32.0)	
	Don't receive Aspirin	151 (36.5)	109 (29.3)	
Usage of Aspirin as protective from blood coagulation	Yes	220 (53.1)	240 (64.5)	0.020*
	No	194 (46.9)	132 (35.5)	
Other drugs used with Aspirin	Antihypertensives	60 (14.5)	86 (13.7)	0.008*
	Treat Dyslipidemia	27 (6.5)	72 (19.4)	
	Treat Diabetes	39 (9.4)	62 (16.7)	
	Received Aspirin only	12 (2.9)	10 (2.9)	
	Don't receive drugs	276 (66.7)	222 (59.7)	
Indication of Aspirin as protective from	MI	102 (24.6)	135 (36.3)	0.007*
	Brain Stroke	57 (13.8)	62 (16.7)	
	IHD	55 (13.3)	72 (19.4)	
	DVT	27 (6.5)	34 (9.1)	
	After Cardiac Surgery	25 (6.0)	33 (8.9)	
	Clots in Pulmonary artery & peripheral arteries	22 (5.3)	33 (8.9)	
	TIA	24 (5.8)	20 (5.4)	
	Stroke in coronary artery	23 (5.6)	20 (5.4)	
	Analgesic	89 (21.5)	72 (19.4)	
	Don't receive Aspirin	151 (36.5)	(29.3)	

*Significant difference at p value <0.01

Good efficacy of Aspirin was reported by 55.1% & 65.3% (Table 3). The signs of aspirin un-efficacy were varied such as frequency of DVT (~ 3%), stroke in coronary artery (~ 4%), brain stroke (3.9% & 5.6%), TIA (1.2% & 2.7%), blood clotting (4.3% & 8.9%), MI (3.3% & 11.6%) from Saudis & Egyptians respectively (Table 3) (Figure 1). More than fifty percent of the participants were strongly agreed and agreed (53.7% & 66.2%) of using aspirin as anticoagulant (Table 3) (Figure 2) and 56.5% & 60.8% of participants did not change aspirin to another anticoagulants, only 7.0% & 9.9% who were changing aspirin either from Saudis & Egyptians respectively (Table 3) (Figure 3).

The reasons for changing aspirin by other anticoagulant were varied between participants first, due to aspirin un-efficacy (1.2% & 1.1%) or caused bleeding (1.2% & 2.2%) or gastric ulcer (1.7% & 2.7%) and hypersensitivity (2.7% & 4.0%) from Saudis & Egyptians respectively (Table 3) (Figure 3).

Blood coagulable state was normal in about 95% of participants, while 3.3% vs. 1.1 with low blood coagulation and 1.9% vs. 1.1% with high blood coagulation and only 7.0% & 9.9% was using other anticoagulant plus aspirin, also, physicians (38.6% Vs 39.0%), pharmacists (16.7% Vs 23.6%) and health care providers (8.2% Vs 8.1%) were persons who gave advices to receive aspirin as protective from blood clotting in patients with history of CVDs or CADs either from Saudis & Egyptians respectively (Table 3). There was a significant difference (P value <0.05) between Saudis and Egyptians in all parameters (Table 3).

Table 3 Assessment of some parameters about Aspirin resistance among Egyptian and Saudi population (Total n=786 Participants, n= 414 (Saudis), n=372 (Egyptians))

Question	Answer	Saudis n (%)	Egyptians n (%)	P- value
Aspirin efficacy	Yes	228 (55.1)	243 (65.3)	0.021*
	No	6 (1.4)	4 (1.1)	
	I don't know	180 (43.5)	125 (33.6)	
Signs of Aspirin Un-efficacy	Frequency of DVT	13 (3.1)	13 (3.5)	0.019*
	Frequency of stroke in coronary artery	17 (4.1)	17 (4.5)	
	Frequency of TIA	5 (1.2)	10 (2.7)	
	Frequency of brain stroke	16 (3.9)	22 (5.6)	
	Frequency of blood clotting	18 (4.3)	33 (8.9)	
	Frequency of MI	14 (3.3)	43 (11.6)	
	I don't know	180 (43.5)	125 (33.6)	
	I don't receive Aspirin	151 (36.5)	109 (29.3)	
Agreement of Aspirin efficacy	Strongly agree	57 (13.8)	33 (8.9)	0.020*
	Agree	165 (39.9)	213 (57.3)	
	Neutral	166 (40.1)	94 (25.3)	
	Disagree	12 (2.9)	12 (3.2)	
	Strong disagree	14 (3.4)	20 (5.4)	
Do you change Aspirin	Yes	29 (7.0)	37 (9.9)	0.017*
	No	234 (56.5)	226 (60.8)	
	Don't receive Aspirin	151 (36.5)	109 (29.3)	
Reason for changing Aspirin	Not effective	6 (1.4)	4 (1.1)	0.022*
	Bleeding	5 (1.2)	8 (2.2)	
	Gastric Ulcer	7 (1.7)	10 (2.7)	
	Hypersensitivity	11 (2.7)	15 (4.0)	
	I don't change Aspirin	234 (56.5)	226 (60.8)	
	I don't receive Aspirin	151 (36.5)	109 (29.3)	
Blood Coagulable State	High	8 (1.9)	4 (1.1)	0.023*
	Low	14 (3.3)	4 (1.1)	
	Normal	392 (94.7)	364 (97.8)	
Using other anticoagulant plus Aspirin	Yes	29 (7.0)	37 (9.9)	0.010*
	Received Aspirin only	234 (56.5)	226 (60.8)	
	Don't receive Aspirin	151 (36.5)	109 (29.3)	
Who advised you to received Aspirin?	Physicians	160 (38.6)	145 (39.0)	0.032*
	Pharmacists	69 (16.7)	88 (23.6)	
	Health care providers	34 (8.2)	30 (8.1)	
	Don't receive Aspirin	151 (36.5)	(29.3)	

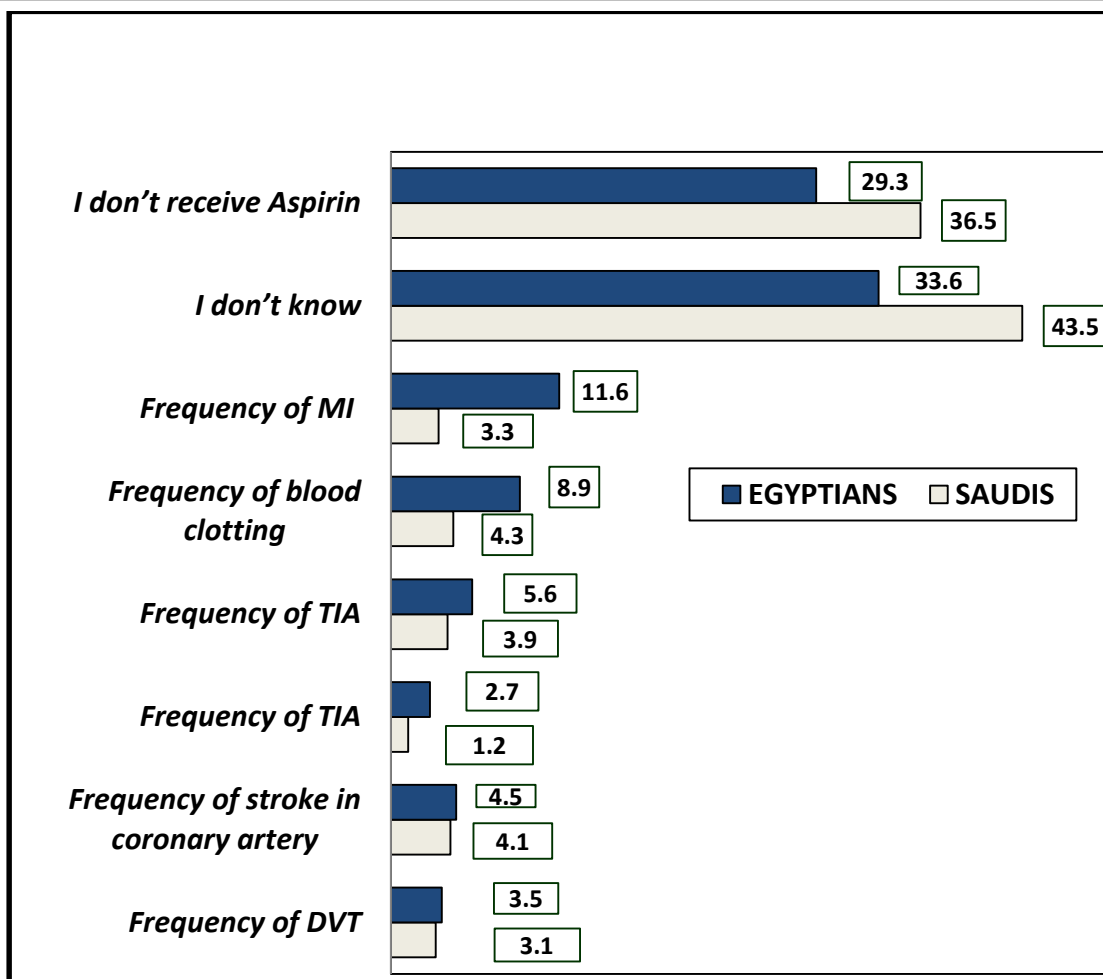*Significant difference at p value <0.01

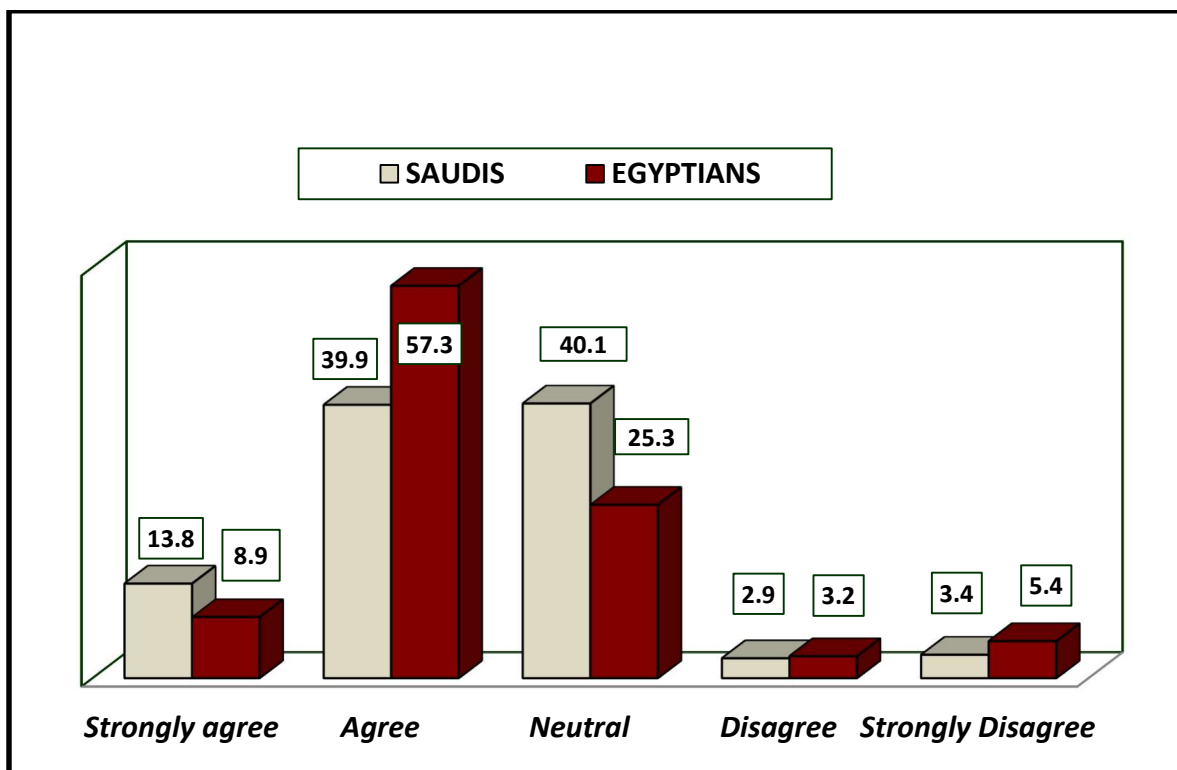**Figure 1** Signs OF Aspirin Un-Efficacy among Saudi and Egyptian Participants (%)

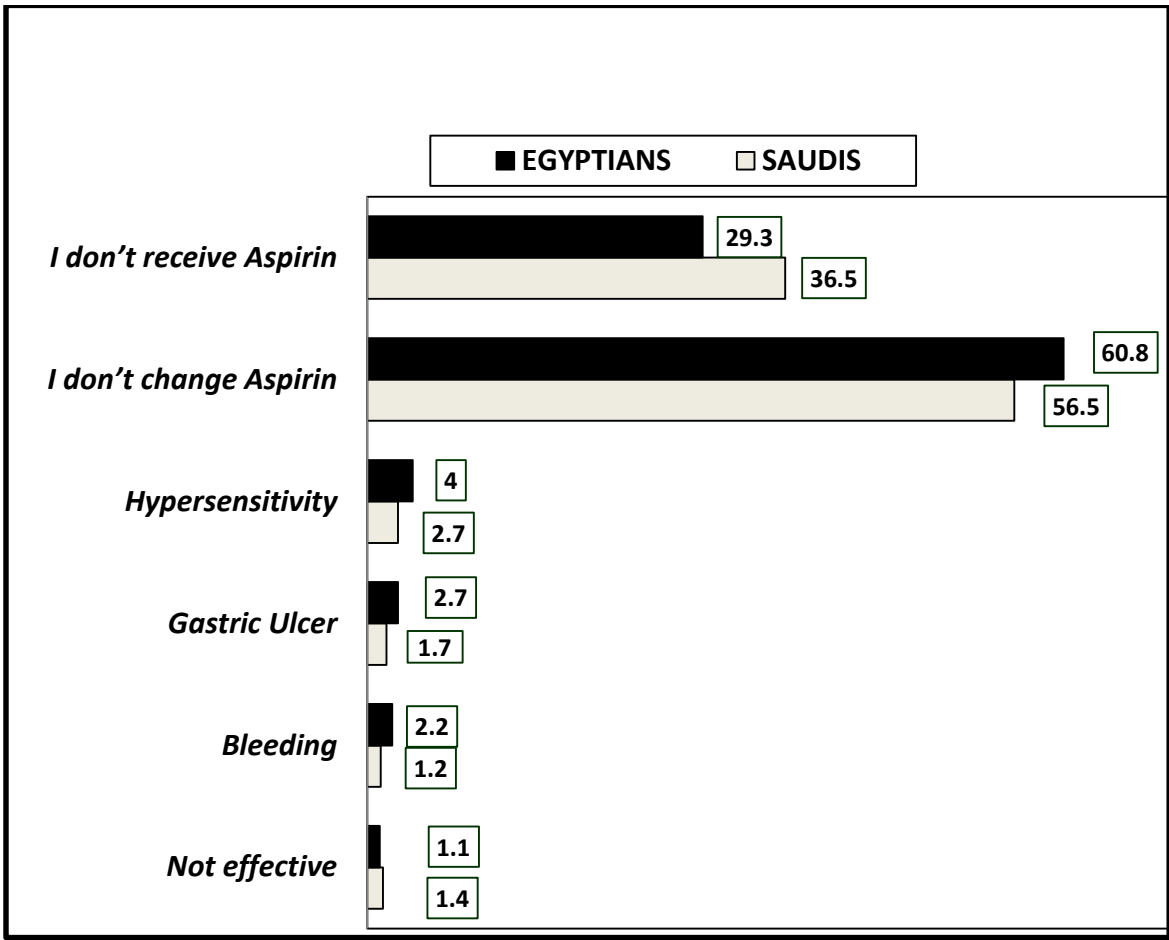**Figure 2** Agreement OF Aspirin efficacy among Study Groups

Figure 3 Reasons for Changing Aspirin to another Anticoagulants among Saudi and Egyptians Participants (%)

4. DISCUSSION

Despite the emergence of new antiplatelet drugs in the last decade, aspirin remains the most widely used agent for the prevention of cardiac diseases. The long-term administration of aspirin to patients with high cardiovascular disease risk results in a 25% decrease in cardiovascular diseases (including TIA and stroke and death), a 48% decrease in bypass surgery and arterial thromboembolic events, a 67% decrease in pulmonary embolism events and a 67% decrease in deep vein thromboses. Thrombotic vascular events can develop, despite aspirin treatment and this phenomenon has been termed aspirin resistance. There is no standardized test for the detection of aspirin resistance; platelet function tests indicate a prevalence of 5.5 – 60% in adults (Ali et al., 2023).

In another study the occurrence of aspirin resistance in a group of 360 Chinese patients using various laboratory tests (Poulsen et al., 2007; Khan et al., 2023). In our study is has showed that good efficacy of Aspirin was reported by 55.1% & 65.3%. The signs of aspirin un-efficacy were varied, but all reasons happened with few cases such as frequency of DVT (~ 3%), stroke in coronary artery (~ 4%), brain stroke (3,9% & 5.6%), TIA (1.2% & 2.7%), blood clotting (4.3% & 8.9%), MI (3.3% & 11.6%) from Saudis & Egyptians respectively.

Current guidelines recommend dual-antiplatelet therapy with aspirin and a P2Y12 inhibitor in patients with AMI. However, in some studies in patients with DM, there is a blunted response to treatment, in which platelet activation persists even with the use of antiplatelet agents (Ferguson et al., 2008). From the Past studies it is noted that the decreased effect of aspirin in acute coronary syndromes has many reasons and positive association with obesity, MI, Citrate smoking and diabetes Mellitus.

In our study more than half of the participants were strongly agreed using aspirin as anticoagulant and more than half of the participants did not change aspirin to other anticoagulants, only few who were changing aspirin either from Saudis & Egyptians respectively. In another study there is 2-year follow up of 326 stable cardiovascular patients from 1997 to 1999 on 325 mg daily aspirin, 17 (5.2%) aspirin resistant (Venketasubramanian et al., 2011) patients defined by optical aggregometry had an increased risk of mortality and cardiovascular risk compared with patients who were aspirin sensitive (24% vs. 10%). Use of Aspin in varicose vein is studied and efficacy is prove by various studies.

Increased doses of aspirin have a dose-dependent effect on platelet agreeability, based on studies in stroke patients using daily doses of 40 mg to 1.3 g (Birschmann et al., 2008). Our study used a fixed dose of 100 mg, which is within the range recommended by local and international guidelines in our studies the prevalence of using aspirin was is highly enough and mote in Egyptian than from Saudis respectively. Livak and Schmittgen, (2001) and Aboelnaga et al., (2020) concluded that Aspirin for primary prevention reduces nonfatal ischemic events but significantly increases nonfatal bleeding events.

Aspirin, as a typical antiplatelet therapy for secondary stroke prevention (Wang et al., 2022; Zhao et al., 2021). In our study aspirin un-efficacy were wide-ranging, but all reasons happened with few cases such as frequency of DVT, stroke in coronary artery, brain stroke, TIA and blood clotting event with prolong use of aspirin.

5. CONCLUSION

From our results we can conclude that low percentage of aspirin resistance was observed among patients using aspirin as anticoagulant either in Saudis or Egyptian patients. More research was needed to be done on more patients to confirm these results.

Author Contributions
MRM and FK, conceptualization, supervision, work design, reviewing relevant literature, analysis and writing and editing the scientific paper; STMA & AFSA, conceptualization, data collection from Saudi Arabia, work design, reviewing relevant literature, and writing and editing the manuscript; FKZB and AFAA, work design, reviewing relevant literature, analysis and writing and editing the scientific paper; SGA & OGA conceptualization, data collection from Egypt, work design, work design, reviewing relevant literature and writing and editing the manuscript. All authors read and approved the final manuscript.

Ethical Approval
This study has been reviewed and approved by the research Ethical Committee (REC) at the University of Hail research number (H-2022-350) dated 31/10/2022.

Informed consent
Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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