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Evaluation of Management of Patients with Cardiovascular Diseases on Acetylsalicylic Acid (Aspirin) as Antiplatelet

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Abstract

Low-dose aspirin is currently used for the prevention of thrombotic patients with pre-existing cardiovascular disease. Patients who failed to respond aspirin are classified as "Aspirin Resistant" (AR). Evaluate the prevalence of pharmacological resistance as a result of aspirin therapy through observation of clinical events. It was a prospective observational study carried on a total of 211 (32-89yr, 50-126.9 kg) patients on 81 mg aspirin. The cardiovascular events were monitored by cardiac risk assessment for each patient during 18 months. (after 3 months, 6 months 12 months and 18 month).The results showed that prior to the study period 40.70% of participants did not use aspirin in a proper way. Aspirin resistance was detected in 7.11% after 3 months that progressively increased to 40.76% after 6 months then to 71.09% after 12 months and to 76.78% after 18 months. The study also revealed that most of the participants who were aspirin resistant retained one or more of CAD risk factors such as those with family history of CAD (68.72%), smoker (75.83%), CAD events (24.64%),pre exposed to had heart surgeries (70.14%), other diagnosis; with hypertension, diabetes mellitus and dyslipidemia collective presented 72.99 %. Also there were other factors such as chronic kidney disease 2.84%, GIT ulcer 10.90%. Study showed that consumption of NSAID by 8.08%.The study showed that 162 out of 211 participants were having CAD event which may be due to "Aspirin resistant" 76.78% and the remaining 23.22% were considered as "non-Aspirin resistant".

Key words: Coronary artery disease (CAD),Nonsteroidal anti-inflammatory drug(NSAID), Gastrointestinal tract (GIT), cardiovascular events (CVE)

INTRODUCTION:

CVDs are the number one cause of death globally: more people die annually from CVDs than from any other cause.
An estimated 17.5 million people died from CVDs in 2012, representing 31% of all global deaths. Of these deaths, an estimated 7.4 million were due to coronary heart disease and 6.7 million were due to stroke .
Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels and they include:

- coronary heart disease
- cerebrovascular disease
- peripheral arterial disease – disease of blood vessels supplying the arms and legs;
- rheumatic heart disease
- congenital heart disease deep vein thrombosis and pulmonary [1]

Coronary artery disease (CAD) is the leading cause of mortality in the world, also known as ischemic heart disease (IHD) is a group of diseases that includes: stable angina, unstable angina, myocardial infarction, and sudden cardiac death. Its' condition in which imbalance between myocardial oxygen supply and demand, most often caused by atherosclerosis of the coronary arteries, results in myocardial hypoxia and accumulation of plaque.
Acute coronary syndromes (ACS): life-threatening conditions that encompass a continuum ranging from unstable angina (UA) pectoris to the development of a large acute myocardial infarction (MI), a condition of irreversible myocardial necrosis.
Atherothrombosis has long been recognized as a key contributor to cardiovascular (CV) events such as myocardial infarction (MI), unstable angina (UA), stroke, and transient ischemic attack (TIA). Given the important role of platelets in acute thrombus formation, antiplatelet therapies have become one of the cornerstone treatments of these atherothrombotic syndromes.[2]
At the end of the 19th century as a synthetic analgesic agent with improved gastric tolerability vs. naturally occurring salicylates, acetylsalicylic acid (marketed as aspirin in 1899) turned out to be an ideal antiplatelet agent about 90 years later, following the understanding of its mechanism of action, the development of a mechanism-based biomarker for dose-finding studies, and the initiation of a series of appropriately sized, randomized clinical trials to test its efficacy and safety at low doses given once daily. At the turn of its 110th anniversary, aspirin continues to attract heated debates on a number of issues including (i) the optimal dose to maximize efficacy and minimize toxicity; (ii) the possibility that some patients may be 'resistant' to its antiplatelet effects; and (iii) the balance of benefits and risks in primary vs. secondary prevention [3].
In general a population with no history of previous myocardial infarction or stroke, aspirin also seems useful for primary prevention of cardiovascular events. Long-term aspirin administration in patients at high risk of occlusive vascular events recent review trials had significant reductions in risk of a first MI (32%) and important vascular events (15%). For secondary cardiovascular prevention, the net benefits of adding aspirin to other preventive measures would substantially exceed the bleeding hazards, irrespective of age and gender. In contrast, for many people without pre-existing vascular

disease, the cardiovascular benefits of adding long-term aspirin to other, safer, forms of primary prevention.[5-6]

In patients who have had a myocardial infarction or revascularization procedure, secondary prevention of coronary artery disease by comprehensive risk factor modification reduces mortality, decreases subsequent cardiac events, and improves quality of life. Options for secondary prevention include medical therapy and surgical revascularization in the form of coronary artery bypasses grafting or percutaneous coronary intervention. Medical therapy focuses on comprehensive risk factor modification. Therapeutic lifestyle changes (including weight management, physical activity, tobacco cessation, and dietary modification) [2]

Low dose aspirin (75-150 mg daily) is an effective antiplatelet regimen for long term use, but in acute settings an initial loading dose of at least 150 mg aspirin may be required. Adding a second antiplatelet drug to aspirin may produce additional benefits in some clinical circumstances, but more research into this strategy is needed. [7]

An inadequate response to prescribed aspirin is a common clinical problem with estimates of prevalence ranging from 4% to 83% with a consensus average of about 25%., some studies published study identified a variable, assay-dependent frequency of non-responder samples, ranging from aslowas1.4% to 30%., other study estimated that 5.5%–60% of the population does not respond adequately to aspirin therapy [8-9]

In the Middle East and Gulf region the awareness of aspirin resistance is very rarely, there is no specific blood test to discover (AR).we need more devices to test platelet function (and these are now being applied mainly to assess antiplatelet drug efficacy in thrombotic disorders). Clinical causes of aspirin resistance can range from patient non-compliance to physicians who display aspirin resistance, that is, physicians who fail to prescribe aspirin appropriately, they must emphasize on proper patients compliance, as well as avoidance of potential drug-drug interactions [10].

In Gulf region the awareness of aspirin resistance is very rarely, there is no specific blood test to discover (AR). For patients who had CAD if complications appear.The physicians' build their decision patient history, physical examination and evaluation of routine blood test, and then they will put their recommendation according to syntax score for ACS.

METHODS

Study design

Prospective cross sectional hospital based observational study.

Study area:

Kingdom of Saudi Arabia Eastern region in Almana General Hospital (AGH)- Khobar & Dammam.

Population:

Patients of either sex of age group 32-89 with body weight between 50-126 kg admitted or visited cardiologists in Outpatient clinic in the hospital and they were on Aspirin as prophylaxis antiplatelet for primary or secondary prevention of coronary artery disease or other diseases.

Sample Size:

211 males and females, despite the gender the sample size chosen according to cross sectional studies to estimate a population who suffered from primary or secondary CAD, formula for qualitative variable were used

$$\text{Sample size} = \frac{Z_{1-\alpha/2}^{2}\, p(1-p)}{d^2}$$

Inclusion criteria:

- Age 32-89 years old
- Weight 50-126 kg
- All Patients receiving Aspirin since April 2014-June 2016 for cardiovascular or coronary artery disease either for primary or

secondary prevention or after CABG or PCI as following criteria:

- aspirin alone 81 mg once daily, or
- aspirin 81 mg once daily in combination with other antiplatelet drugs such as clopidogril 75mg once daily or
- aspirin 81 mg once daily in combination with Ticagrelo 90 mg twice daily and they were suffering from CVD, formula for qualitative variable were used

Exclusion criteria:

- Patients who made CAG, PCI, CBAG or other heart surgery for more than 10 years.
- Need for anticoagulant treatment
- Current or administration of other thienopyridines or ADP receptor inhibitors
- Known thrombocytopenia (<100.000 / μL)
- Known allergy to Aspirin, clopidogrel or ticagrelor
- Recent (< 6 weeks) major operation, including CABG
- History of bleeding disorders
- Known intracranial mass, arteriovenous shunt or aneurism
- Previous intracranial bleeding
- INR>1.5
- Other clinical conditions associated with increased bleeding risk, according to the investigators' judgment.

Data collection:

The effectiveness of regular aspirin (secondary prevention) therapy in reducing risk of myocardial infarction, ischemic stroke, and fatal coronary events among persons with preexisting atherosclerotic cardiovascular disease. (211) patients with a history of coronary events (CAD) were identified by review of medical records and were contacted for the study.

Forms for data collection will be filled every three months during patients follow up (after 3 months, 6 months, 12 months, and 18 months) to observe the stability of their conditions to avoid any risk of CAD events during receiving Aspirin 81 mg alone or in combination of Clopidogrel or Ticagrelor.

If any fetal CAD events will appear the patient will go through physical examination and evaluation of routine blood test and cardiac risk assessment procedure then they will put their recommendation according to syntax score for ACS.

Physical examination such as;

- Echocardiography
- Electrocardiography (EKG =electrocardiogram),
- Chest X Ray,
- Diagnostic and Imaging Studies**,** MRI,
- CT Cardiac Computed Tomography Angiography
- Evaluation of routine blood test : Abnormal results from blood tests Cardiac enzymes (including troponin and creatine kinase), C-reactive protein (CRP), fibrinogen, homocysteine, lipoproteins, triglycerides, brain natriuretic peptide (BNP) and prothrombin.

Pharmacologic stress test,

Cardiac catheterization: CAG (Coronary angiography) is a test that uses dye and special x rays to show the insides of coronary arteries)

Physician's recommendation will build according to syntax score ((i.e an angiographic tool grading the complexity of coronary artery disease). Higher SYNTAX scores, indicative of more complex disease are hypothesized to represent a bigger therapeutic challenge and to have potentially worse prognosis of (acute coronary syndrome) to proceed, PCI (Percutaneous Coronary Intervention) or CABG (Coronary Artery Bypass Grafting using saphenous vein or internal mammary artery).

In acute coronary syndromes and after coronary stenting, flow cytometric analysis of platelet activation dependent markers predicts major adverse cardiac events (MACE).

The patients' they were divided into 2 groups:

Category I: patients without CAD events with long/ or short -term aspirin therapy; patients received Aspirin 81 mg once daily for primary prevention from CAD events and they may have one or combination of these disease, hypertension, diabetes, dyslipidemia

Category II: patients with CAD events, received 81 mg aspirin once daily before the cardiac procedure either alone or in combination with other antiplatelet (Clopidogre or Ticagrelor)

If any patient from Group I or Group II went through cardiac procedure , they he will continue receiving Clopidogrel 75 mg once daily or Ticagrelor 90 mg twice daily plus Aspirin 81 mg once daily.

All patients who had drug-drug, food or diseases interaction were discussed with the physicians for management.

Any symptoms for any side effects were managed during patients follow up.

- **Blood samples:**

The physicians requested for some patients cardiac enzymes such as CK-MB and troponin**.** Other blood tests such as bleeding time (BT), thrombine time (TT), prothrombine time (PT), activated partial thromboplastin time (APTT) and international normalized ratio (INR). Most of blood tests were done when patients went for cardiac procedure.

Data Analysis :

All data were analyzed using statistical Package for the Social Sciences (SPSS) V.21.

Ethical consideration :

Hospital permission was taken, all patients were informed about the nature of study and a written consent obtained for all of them. All patients were informed that their participation in study is voluntary. No names attached to the forms.

RESULTS:

Two hundred and eleven (211) either sex were participated in the study. The sample size were chosen according to patients who had coronary artery disease or others risk factor diagnosis admitted through ER or came to outpatient clinics and receiving maintenance doses 81mg of Aspirin alone as antiplatelet or in combination with other antiplatelet (Clopidogre or Ticagrelor) for primary prevention or secondary prevention this study were started from April 2014- June 2016. (Table 1).

Table 1: Distribution of patients according to gender

Gender	Patient No#	Percent%
Male	187	88.6%
Female	24	11.4%
Total	211	100%

Table 2: Distribution of patients according age group

Age group	No# of patients	percent %
30-48 years	60	28.44%
49-58 years	81	38.39%
59-68 years	48	22.75%
69-89 years	22	10.43%
Total (n)	211	100%

The 211 patients participated in this study. Socio-Demographic characteristics of patients were predominantly in age group between (32-89 years old), their weight between (50-126.9 kg). (Table 2 & 3)

Table 3: Distribution of patients according weight group

Weight group	No# of population	Total %
GRP1=50-70 kg	70	33.18%
GRP2=71-90 kg	102	48.34%
GRP3=91-110 kg	33	15.64%
GRP4=ABOVE 111 kg	6	2.84%
Total (n)	211	100%

At the beginning of the study 55.92 % of the patients who participated in the study on aspirin 81mg once daily alone and 44.08% with combination of either Clopidogrel or Ticagrelor (Table 4)

Table 4 Distribution of patients according to antiplatelet used at the beginning of study

Category	Frequency	Percentage
Category I ASP ALONE	118	55.92
Category II (aspirin with another antiplatelet)	93	44.08
Total	211	100%

Before conducting the study we made patient's education to ensure that they follow the proper way to take their aspirin dose as prescribed as well the others medicines, we found that (59.24%) were compiled and (40.76%) were not complied to take their medicines.(Table 5) N.B. Patient adherence not done.

Table 5: Patients' compliance

Patient criteria	No# of patients	% of compliance
Compliant	125	59.24%
Non-compliant	86	40.76%

80.57% was the average percentage of patients who had family history of CAD overall patients and (19.43%) had no family History with CAD. (Table 6)

Table 6: Distribution of patients according to family history of CAD

Criteria	No of Patients	% of patient
Patients with family history	170	80.57%
Patients with no family history	41	19.43%
Total	211	100%

The patients who participated in the study had smoking habit, (87.2%) smokers and (12.8%) nonsmokers.(Table 7) Out of 211only (120 patients) did some blood function tests, the result showed that the highest percent (56.87%) for the tests which done, and (91 patients) 43.13% the physicians didn't request for them any. Those because they depend on other cardiac risk assessment so not all tests were performed. Also most of results showed the normal values regardless for those who went for cardiac surgeries. (Table 8)

Table 7: Distribution of patients according to smoking habit

Gender	Smoker	Total percent %	Non-smoker	Total percent %
Male	181	85.78%	6	2.84%
Female	3	1.42%	21	9.95%
Total	184	87.20%	27	12.80%

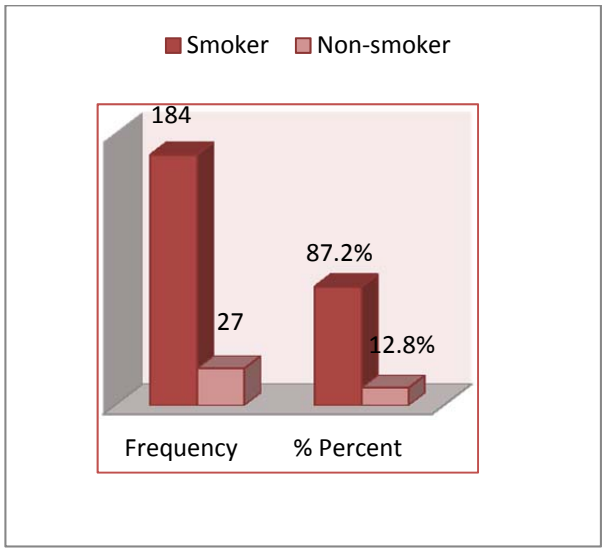

Figure 1: Distribution of patients according to smoking habit

Table 8: Blood Function tests and cardiac enzymes

Test	Normal	%	High	%	Low	%	Not done	%	Total no. Patients
BT	35	16.59	2	0.95	0	0.00	174	82.46	211
APTT	66	31.28	32	15.17	17	8.06	96	45.50	211
TT	74	35.07	12	5.69	14	6.64	111	52.61	211
PT	97	45.97	13	6.16	3	1.42	98	46.45	211
INR	12	5.69	2	0.95	1	0.47	196	92.89	211
FIB	44	20.85	56	26.54	4	1.90	107	50.71	211
CK-MB	15	7.11	9	4.27	0	0.00	187	88.63	211
Troponin	8	3.79	11	5.21	0	0.00	192	91.00	211

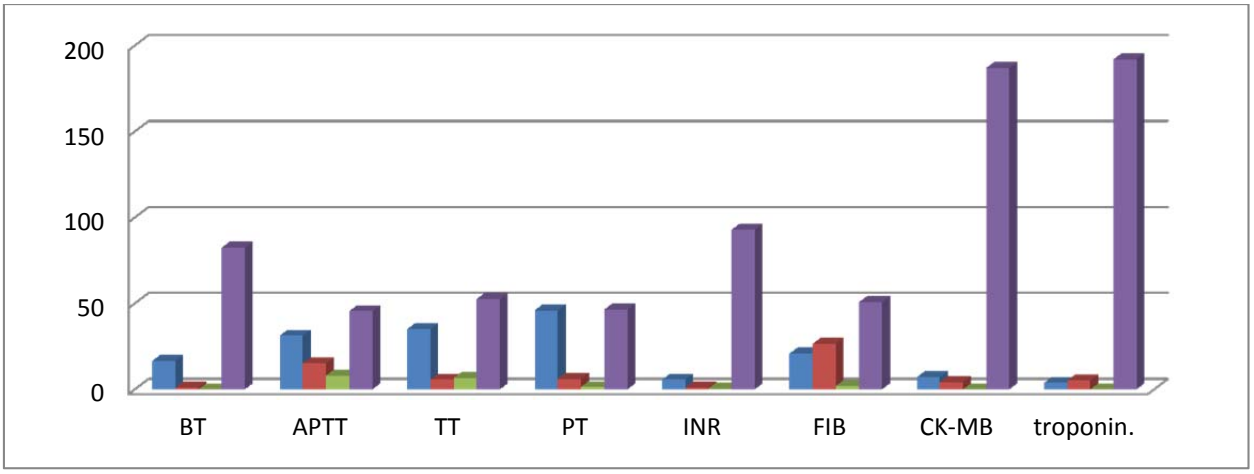

Figure 2: Blood Function tests and cardiac enzymes

Table 9: Patients on aspirin for primary prevention of CAD

Patient (n=86)			Collective Total %
Current diagnosis	**Patients' diagnosis #**	**% of patients' diagnosis**	
HTN+DM+DSL,	17	8.06	24.64%
HTN,	11	5.21	
HTN+DM	4	1.90	
HTN+DSL	10	4.74	
DM+DSL	2	0.95	
DM	5	2.37	
DSL	3	1.42	
Other diseases			
CKD	2	0.95	0.95%
GIT ulcer	15	7.11	7.11%
Medications			
NSAID	7	3.32	3.2%
Diuretics	42	44.55	44.55%

Table 10: Patients on Aspirin for secondary prevention of CAD

Patient (n=125)			
Current diagnosis	**Patients' diagnosis #**	**% of patients' diagnosis**	**Collective Total %**
Unstable Angina	13	6.16	24.64%
STEMI	8	3.8	
NSTEMI	3	1.42	
HF	4	1.9	
CCF	1	0.47	
AF	2	0.95	
Chest pain	10	4.74	
Shortness of breath	10	4.74	
ASD	1	0.47	
Urgent PCI	23	10.9	10.90%
Risk factors			
HTN+DM+DSL	30	14.22	56.87%
HTN	31	14.69	
HTN+DM	14	6.64	
HTN+DSL	19	9	
DM+DSL	2	0.95	
DM	12	5.69	
DSL	12	5.69	
Other diseases			
CKD	6	2.84	2.84%
GIT ulcer	28	13.27	13.27%
Medications			
NSAID	20	9.48	13.27%
Diuretics	94	44.55	44.55%

40.76% (n=86) out of 211 patients on Aspirin 81 mg once daily for primary prevention of CAD, diagnosed by one or more of these diseases; hypertension, diabetes diagnosis mellitus, dyslipidemia, chronic kidney disease, GIT ulcer and on medications such as NSAID and diuretics. (Table 9)
59.29% (n=125) out of 211 patients, they diagnosed with CAD events, urgent PCI, and one or more of these diseases; hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, GIT ulcer and on medications such as NSAID and diuretics.. All these patients on Aspirin 81 mg once daily for secondary prevention of CAD (Table 10)

No major drug interaction, most drugs which have interaction and used by the patients are: Calcium / vitamin d, Rosuvastatin, Duloxetine Insulin glargine, Furosemide, Atorvastati, Metoprolol Succinate**,** Amlodipine, Clopidogrel, Ticagrelor, Omeprazole, and Acetaminophen.

No Food interaction, alcohol not found and only 40% from the participant were drinking coffee with minor interaction.

The patients who had CAD events underwent to cardiac interventions or surgeries, such as (PCI, or CABG, PTCA or inserting devices). The percentage was increased from

60.2% to 70.14%, the remaining percentage didn't make any.(See Table 11).

The previous results concluded the main risk factors or diagnosis behind Aspirin resistance like family history of CAD smoking such as CAD events, exposure to previous heart surgeries or urgent PCI and other diseases like diabetes mellitus, hypertension, dyslipidemia, and other such as chronic kidney and GIT ulcer. The result showed also some medications such as; NSAIDs and diuretics were used.

During the study period (3 months for each patient), we monitored the patient's response to aspirin. The results showed different responds to Aspirin according to the study periods (3 months, 6 months, 12 months and 18 months) (See table 12).

This comparison for primary and secondary at the end of study, showed that some patients who had primary prevention and had risk factor developed CAD events, also around 99 % from patients who had CAD events or previous cardiac procedures developed secondary CAD events and went for another PCI or CABG.

Table 11: Distribution of patients according to cardiac interventions or Procedures done

Procedures	Frequency 1st time	% of 1st time	Frequency 2nd times	% of 2nd time	Total Frequency	Total % Percentage
PCI	93	44.08	12	5.69	105	49.76
CABG	12	5.69	9	4.27	21	9.95
Other procedures PTCA or inserting devices	22	10.43	0	0	22	10.43
Total	127	60.2	21	9.95	148	70.14

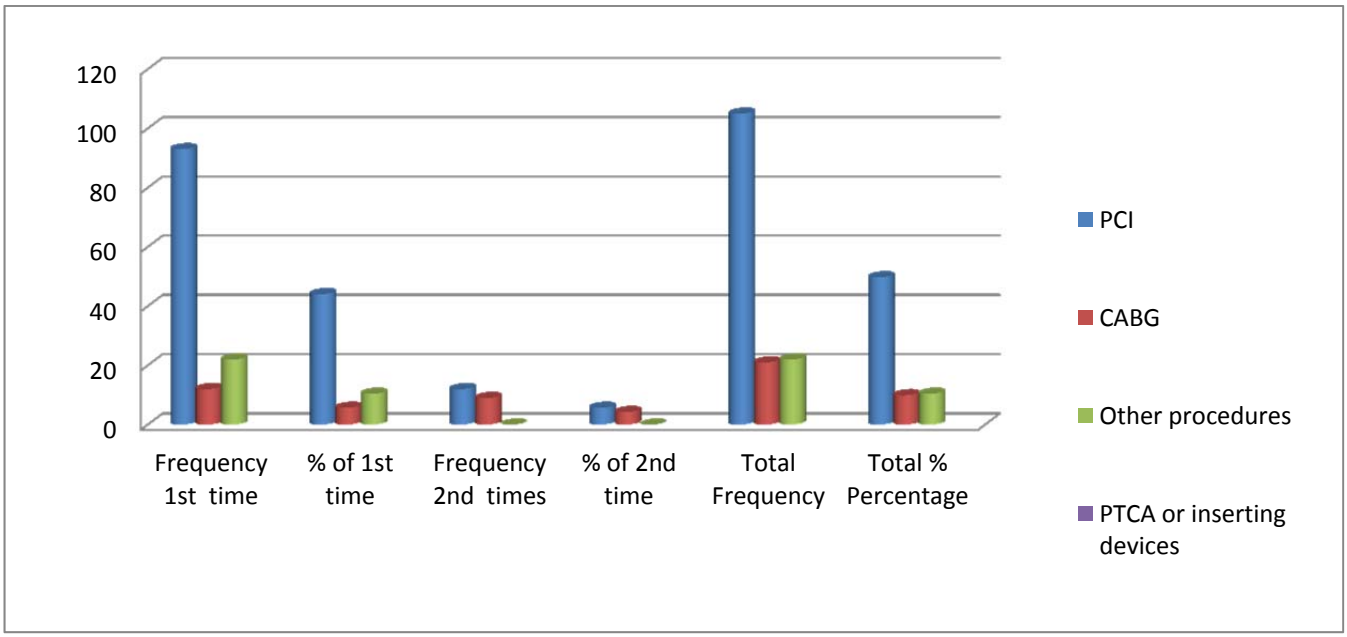

Figure 3: Distribution of patients according to cardiac interventions or Procedures done

Table12: Distribution of patients according to their response to aspirin during study period

No. of patients (n=211)	After 3 months (n=211)		After 6 months (n=196)		After 12 months (n=125)		After 18 months (n=62)	
	Responded	Not responded	Responded	Not responded	Responded	Not responded	Responded	Not responded
NO# Patients	196	15	125	71	62	63	49	13
total No#	196	15	125	86	63	149	49	162
Total % of Patients	92.89%	7.11%	59.24%	40.76%	29.58%	70.62%	23.22%	76.78%

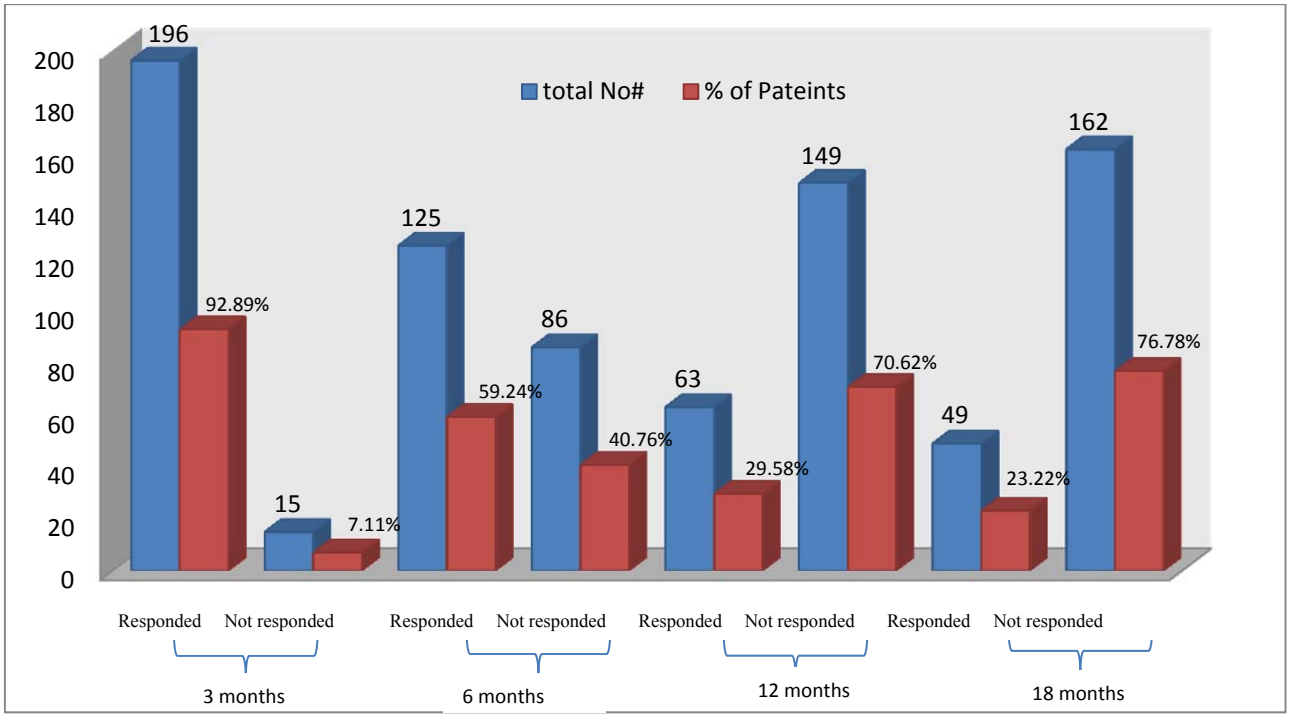

Figure 4: Distribution of patients according to their response to aspirin during study period

Table 13: Comparison for primary and secondary patients' responds to aspirin during study period

	Predictors	Responded	Percent %	Non responded	Percent %
Primary	Family History	18	8.53	145	68.72
	Smoking	24	11.3	160	75.83
	HTN+DM+DSL	18	8.53	154	72.99
	CKD	2	0.95	6	2.84
	GIT ulcer	20	9.84	23	10.9
	NSAID	10	4.74	17	8.06
	Diuretics	19	9	17	8.06
Secondary	CAD events	0	0	52	24.64
	PCI, CABG, PTCA	0	0	148	70.14

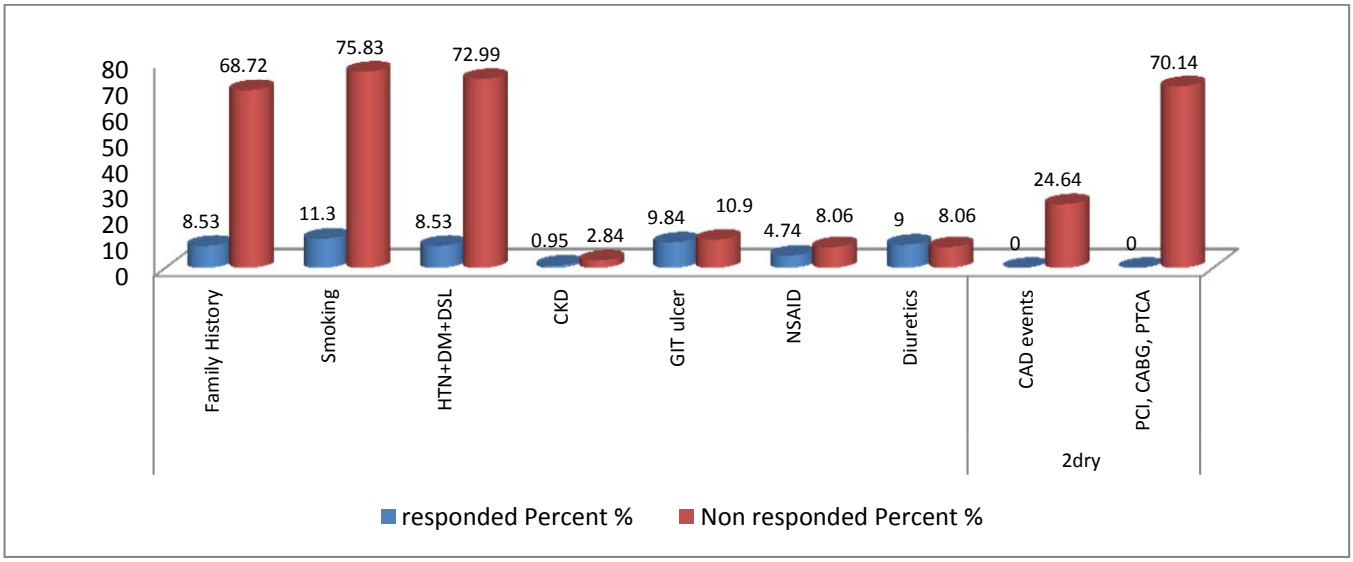

Figure 5: Comparison for primary and secondary patients' responds to aspirin during study period

To measure the response of aspirin for the patients who received Aspirin for primary CAD prevention, or secondary episode of CAD events the patients were divided into two categories according to antiplatelet used. **category I** patients who remained without (CAD) events , they were (23.22%) they remained on aspirin 81 mg alone once daily and **category II** (76.78%) had complications which may be due to "aspirin resistance" (AR), they were on aspirin with another antiplatelet after surgeries. The antiplatelet used in combination with aspirin either Clopidogrel or Ticagrelor.
The result showed 7 patients have resistant event to Clopidogrel, physicians shifted them to Ticagrelor. (Table 14)

Table 14 Distribution of patients according to antiplatelet used at the end of study

Antiplatelet used	Frequency	Percentage %
Aspirin alone	49	23.22
Aspirin+ Clopidogrel	55	26.07
Aspirin +Ticagrelor	107	50.71
Total	211	100.00

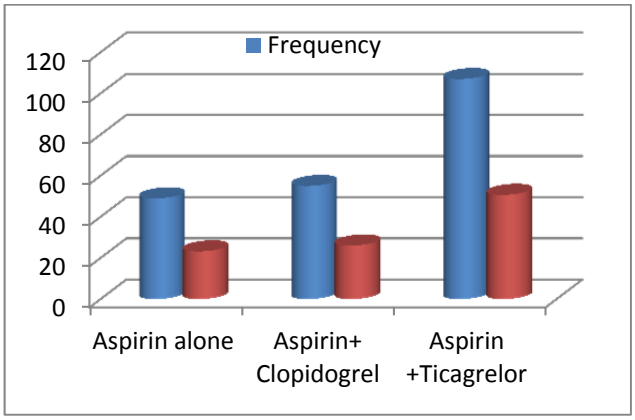

Figure 5: Distribution of patients according to antiplatelet used at the end of study

Finally there were different results according to role of aspirin in primary and secondary prevention which may be showed 23.22% for those who didn't develop CAD events vs. 76.78%. for those who developed CAD events was (see Table 3.1)
As shown in Table 13, aspirin resistance was found to be significantly higher in patients with a family history of CAD (68.72% vs. 8.53%, p =0.011), smoking (75.83% vs. 11.37%, p =0.014), CAD events (24.64% vs. 0.00%, p =0.014), PCI, CABG & PTCA (71.990.14 vs. 0%, p= 0.0001). Moreover, aspirin resistance was found to be more evident among hypertension Diabetes &, Dyslipidemia (72.99% vs. 8.58%, p=0.0032). No statistical differences were observed for parameters like CKD, NSAID and Diuretics

Table 5: Comparison for patient's responses to aspirin during study period

Patients' response (n= 211))	Total number	Percent %
Without (CAD) events remained on Aspirin	49	23.22%
With (CAD) events on Aspirin + other anticoagulants	162	76.78%

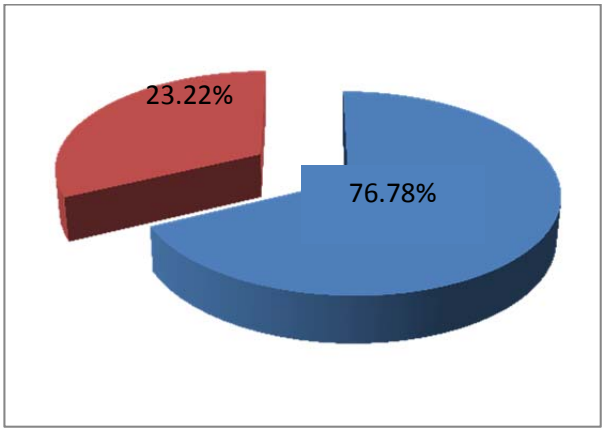

Figure 6: Comparison for patient's responses to aspirin during study period

Table 15 Cross tabulation for Clinical outcome among AR and non-AR patients

Parameter	Total (n=211)	Non Aspirin resistant N AR(n=49)	% of N. AR	Aspirin resistant AR (n=162)	% of AR	P value	P-Value (Z-test)
Age/ weight	(n=211)	35 ± 8.5 yrs 55± 15 Kg		32 ± 10.5 yrs 61± 22 Kg		-	-
Family History	163	18	8.53%	145	68.72%	0.011*	0.00110*
Smoking	184	24	11.37%	160	75.83	0.014*	0.00120*
CAD events	52	0	0.00%	52	24.64%	0.0014*	0.0014*
PCI, CABG, PTCA	148	0	0.00%	148	70.14%	0.0001*	0.000127*
HTN+DM+DSL	172	18	8.53%	154	72.99%	0.0032*	0.00114*
CKD	8	2	0.95%	6	2.84	0.244	0.244
GIT ulcer	43	20	9.48%	23	10.90	0.08	0.08
NSAID	27	10	4.74%	17	8.06	0.9	0.9
Diuretics	136	19	9.00%	17	8.06	0.89	0.89

DISCUSSION

The aim of this study was to evaluate and management the failure of aspirin in treatment of coronary artery disease in small group of population leaved in Saudi Arabia.

The study depended on observation and physical examination, EKG (electrocardiogram), exercise stress test, and other cardiac risk assessment which were done for the patients who received aspirin for primary or secondary prevention from CAD events to evaluate and find out any complications further CAD events.

The study included patients diagnosed by CAD and some of them did cardiac interventions surgeries before and remained stable in a period of ≥10 years. Others diagnosed by hypertension, diabetes, dyslipidemia or combination of them.

This study conducted during 18 months for each patient. During follow-up of patients with stable cardiovascular on aspirin therapy, the results showed that patients with higher serious vascular events may had higher aspirin resistance; the result showed 76.78% out of 211 patients may had aspirin resistant. It was a significantly independent predictor of future outcomes in multivariate analysis. The findings were consistent with available studies conducted by different investigators for different participants with weight and age. [19-21]

Regardless the age and weight as our populations were young and elder most of them had the previous diagnosis but those with high risk were the elder patients. The present study revealed that 59.24% of patients were educated and received their protected dose of Aspirin 81 mg once daily "as prescribed" and this percentage increased by time.

Despite the gab in the absence of complete blood test to measure or investigate aspirin reissuance cause for patients who went for urgent interventions surgeries as they suffered from complications (CAD events), the study found that there was a problem either in dose of Aspirin or other factors. Similar studies have evaluate aspirin resistance (AR) by quantitative and qualitative methods [18,20-23,25-26,35,53]

At the beginning of study out of 211 patients (55.92 %) received aspirin 81 mg once daily alone and (44.08%) in combination with Clopidogrel or Ticagrelor. The percentage of patients who received aspirin alone decreased to reach (23.22%) by the end of study. This result may relevant with other study for some patients who need need combination of antiplatelet [62]

The present study revealed that the patients who were compliance and received their protected dose of Aspirin 81 mg remained had better result (59.24%) while others (40.76%) who were noncompliance the percentage of compliance remind constant, but some patients also developed CAD events [61].

Family history and genetic factors may play an important role in aspirin resistance. The present study has shown a significant correlation (P= 0.011) between aspirin resistance and family history. Patients who have family history of CAD were aspirin resistant regardless infestation of platelet receptor genes. A detailed assessment, particularly of first-degree relatives for the presence of CAD and age of diagnosis is imperative when evaluating a patient's risk factor profile the study found a patient with family history of CAD, 68.72 % patients were resistant against 8.53% non-resistant this evidenced by some studies published showed that genetic factor causing aspirin resistance [27-32, 54].

Smoking may cause aspirin resistance as a result of its procoagulative properties. It was proven that smoking increased the risk of CAD and decreases the ability of aspirin to inhibit the platelet aggregation. The present study showed that patients who were aspirin resistant or aspirin semi-responders were likely to be smokers compared with aspirin-sensitive patients. The present study showed (P value =0.014) of aspirin is prevalent in (76.78%) which is consistent with several studies in aspirin resistant population. The significant correlation (p =0.0014) between patients who had CAD events and aspirin resistance developed by time in this prospective study. Similar studies were agreed with the same results [35, 58-59, 55-57, 33-36].

Blood test were done for the patient who did cardiac intervention before or developed CAD events for 1st time as a routine checkup before surgeries and most of them they didn't do it, the result in the present study showed non-significant (p value=0.78). Despite of this result, these patients may showed 'aspirin resistance" [59-60].Majorities of the patients who may have aspirin resistance in aspirin low dose for primary prevention from CAD events, may suffering from diabetes, hypercholesterolemia, hypertension the percentage of risk increased with combination of hypertension with either DM or DSL. So management of hypertension in patients with or without CAD is exceedingly important. Control of blood pressure reduces myocardial oxygen consumption and thereby reduces angina, and it also lowers the incidence of cardiovascular events. Diabetic patients with CAD have a particularly high risk for recurrent cardiovascular events, and they should be targeted for aggressive risk-factor modification. Guidelines of the National Cholesterol Education Program (NCEP) have recommended an LDL cholesterol level >70 mg/dL for all patients with coronary artery or other atherosclerotic disease. Patients whose LDL levels are >100 mg/dL should start pharmaceutical therapy. 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the recommended first-line agents for patients who have CAD and elevated total and LDL cholesterol levels. The result in this study showed a significant correlation (p=0.0032) between patient with one or combination of these disease were non aspirin responded. The same result were observed by some studies suggested an association of aspirin resistance with diabetes, hypertension and hypercholesterolemia,[35,40-44].Another significant correlation between non responded participants to aspirin low dose for secondary prevention or those who did cardiac interventions or heart surgeries such as; PCI, CABG, or inserted devices, most of these patients who may developed aspirin resistant underwent to heart surgeries for first time or second time. These patients were underwent for one of the previous cardiac surgeries required to achieving cardiovascular protection do so with medical

advices, as measured by a point-of-care assay and according to the SYNTAX Score. There were evidences in studies in line with the present study done in Egypt and South Africa concluded that PCI or CABG increased risk of "aspirin-resistance" AR [34, 39].

Chronic kidney disease were recognized to be one of high disease interaction which increased the rate of AR in all population with elderly patients (2.84%) 211 aspirin resistance CKD in end stage. In the present study (p value =0.244) which was not significant in the present study, but many other study were supported this result. [36,40]

This study showed that certain disease such as GIT ulcers was important factor behind aspirin resistance. This finding was not significant (p value= 0.08), but it was complied with some studies already published in literature.[45-47].

All drug interaction were managed in the study by pharmacy department using the electronic system for food and drug –drug interactions and physicians were informed to change any medication which had either major drug or food interaction. Those with minor drug interaction, administration time for drugs and food were managed also in inpatient and outpatient counseling. This study also revealed coadministration of certain drugs like NSAID increased aspirin resistance and others like diuretics delayed aspirin resistance such as Angiotensin I & II which in line with other studies published in literature. [35, 48-49].

Some patients in this study developed antiplatelet resistance when they use aspirin with Clopidogrel after cardiac intervention, they shifted to Ticagrelor, There were evidences in some studies in Saudi Arabia and others countries matching with this result.[33, 43, 51-52]

In Arab countries the knowledge of aspirin resistance is very poor from patient side and from clinicians' practices usually they neglected. Considering all these we argue with our clinicians to highlighted this issue and more intervention should be done for patient compliance and noncompliance to discover if we need to measure Aspirin resistance after prescribing the low dose for primary CAD to avoid the sudden death for the patients when CAD events were progress and aspirin not working because of anyone from the previous reasons.

CONCLUSION

Previous studies have demonstrated clinical importance of "aspirin resistance" AR which has similar frequency in men and women and increases with age (50-89). Risk factors for AR are similar to other atherosclerotic diseases. Patients with risk factor have more risk to develop AR and underwent for cardiac procedures. AR detection needs improving life style for cardiovascular prevention and treatment.

The study showed that causes for aspirin resistance which had been discussed in this study were: risk factors, drug-drug interactions, food drug interaction, and disease interaction. All patients in these population represent main causes of aspirin resistance were received aspirin regularly for cardiovascular prevention with the majority using it for primary prevention.

Overall, 76.78% patients with cardiovascular events were recorded on antiplatelet treatment versus 23.22% without cardiovascular event.

This study may showed that the maximum failure of treatment in primary and secondary CAD (162 patients) from (211 patients) may perceived "resistance", when compliance and other causes managed assured, 23.22 % of these populations showed response to prophylactic by a dose of 81mg aspirin enteric-coated. This result is agreed with other studies which showed that the maximum prevalence of true AR is between (5%-45%).

In conclusion, in our trial involving patients with stable CAD was not found to be superior to aspirin in reducing the risk of the composite end point of ACS which lead to cardiac interventions.

CONFLICT OF INTEREST

The authors declare no conflict of interest in this study.

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