Aspirin Resistance Incidence and its Impact on PCI Results in Patients with Ischemic Heart Disease Regarding; Myonecrosis, Angiographic and Long Term Clinical Outcomes

Thesis submitted for partial fulfillment of
Doctorate (MD)
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Dedication

TO THOSE WHO HAVE BEEN THERE
EVERY STEP OF THE WAY……

MY FATHER
THE VERY BEST PART OF ME.

MY MOTHER
MY IDOL AND MY EVERYTHING.

Mai
THE BEST wife IN THE WORLD.

Hamza
MY son.

I OWE THEM ALL THAT I HAVE BECOME
AND ALL THAT I EVER WILL BE……

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List of abbreviations

AAP	American Academy of Pediatrics Committee
ACC	American College of Cardiology
ACE	Angiotensin Converting Enzyme
ACS	Acute Coronary Syndrome
AF	Atrial Fibrillation
Agg	Aggregation
AHA	American Heart Association
AMI	Acute Myocardial Infarction
AMP	Adenosine Monophosphate
APS	Angiographic Perfusion Score
ARMYDA	Atorvastatin for Reduction of MYocardial Damage during Angioplasty
ASA	Acetyl Slaicylic acid
ATP	Adenosine Triphosphate
BASKET-LATE	Basel Stent Cost-effectiveness Trial-Late Thrombotic Events
BDT	British Doctors Trial
BMI	Body mass index
CABG	Coronary artery bypass grafting
cAMP	Cyclic adenosine monophosphate
CAPRIE	Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events study
cGMP	Cyclic Guanosine Monophosphate
CK	Creatine Kinase

CK MB	Creatine Kinase MB fraction
COX	Cyclooxygenase
CREDO	Clopidogrel for the Reduction of Events During Observation study
CRP	C-reactive protein
CTFC	Corrected TIMI frame count
CURE	Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events
CVS	Cerebrovascular stroke
DES	Drug Eluting stent
DM	Diabetes mellitus
ECG	Electrocardiogram
EPD	Embolic protection devices
ESPS	European Stroke Prevention Study
ESC	European Society of cardiology
FDA	Food and Drug Administration
GI	Gastrointestinal
GP	Glycoprotein
HDL	High density lipoprotein
HF	Heart Failure
HOPE	Heart Outcomes Prevention Evaluation
HOT	Hypertension Optimal Treatment
IDDM	Insulin Dependant Diabetes Mellitus
IHD	Ischemic Heart Disease
INR	International Normalization Ratio

ISIS	International Study of Infarct Survival
IVUS	Intravascular Ultrasound
LAD	Left anterior descending
LCx	Left circumflex
LDH	lactate dehydrogenase
LDL	Low density lipoprotein
LV	Left Ventricle
MACE	Major adverse cardiac events
MI	Myocardial infarction
MITRA	Maximal Individual Therapy in Acute Myocardial Infarction registry
MRI	Magnetic Resonance Imaging
MVD	Multi-vessel disease
NIDDM	Non Insulin Dependant Diabetes Mellitus
NO	Nitric Oxide
NSAID	Non steroidal anti-inflammatory drug
PAD	Peripheral arterial disease
PCI	percutaneous coronary intervention
PCI-CURE	Percutaneous Coronary Intervention-Clopidogrel in Unstable angina to prevent Recurrent Events
PFA	Platelet Function Analyzer
PGE2	Prostaglandin E 2
PGI2	Prostaglandin I2
PGI3	prostaglandin I3

PHS	Physicians' Health Study
PLT	Platelet
PMI	Periprocedural MI
PPP	Platelet Poor Plasma
PRP	Platelet Rich Plasma
PTCA	Percutaneous Transluminal Coronary Angioplasty
RCA	Right coronary artery
RISC	Research Group on Instability in Coronary Artery Disease in Southeast Sweden
RVD	Reference Vessel Diameter
SALT	Swedish Aspirin Low-dose Trial
SD	Standard Deviation
SPAF	Stroke Prevention in Atrial Fibrillation
TFG	TIMI Flow Grade
TIA	Transient Ischemic Attack
TIMI	Thrombolysis in Myocardial Infarction
TPT	Thrombosis Prevention Trial
TVR	Target vessel revascularization
TXA2	thromboxane A2
STEMI	ST segment elevation myocardial infarction
ULN	Upper Limit of Normal
UK-TIA	United Kingdom Transient Ischaemic Attack trial
vWF	von Willebrand factor

WHO	World Health Organization
WHS	Women’s Health Study

Introduction

Antiplatelet therapy is a crucial component of the medical regimen of patients with cardiovascular disease. In particular, aspirin is the most common cardiovascular drug used. It has been slightly more than 100 years since the synthesis, development, and commercialization of acetylsalicylic acid, the most widely consumed drug in the world. It is estimated that 35000 kg are consumed daily in the United States and 6000 kg in the United Kingdom. **(David B Jack., 1997)**. It has been well established that aspirin is beneficial in the management of the acute phase of evolving acute myocardial infarction (AMI), as well as in stable coronary artery disease. **(Fuster V et al., 1993)**.

The Second International Study of Infarct Survival **(ISIS-2)** has shown conclusively the efficacy of 162.5 mg aspirin daily alone for treating of 17,187 suspected patients with AMI with a 35 day mortality rate reduction of 23%. Another meta-analysis demonstrated that aspirin reduced coronary reocclusion and recurrent ischemic events after thrombolytic therapy with either streptokinase or recombinant tissue-type plasminogen activator. **(Roux S et al., 1992)**.

Generally, aspirin in doses of 81 mg (children's tablet) to 325 mg (adult tablet) once a day is recommended for attaining an antiplatelet effect in patients with coronary artery disease. **(Jafri SM et al 1993)**.

Aspirin prevents the formation of thromboxane A_2, a substance that induces platelet aggregation, in platelets. In

contrast, in vascular endothelial cells aspirin prevents the synthesis of prostacyclin, which inhibits platelet aggregation. The different effects of various doses of aspirin on platelet thromboxane A_2 generation and vascular wall prostacyclin production have been extensively investigated. A dose of 160 mg or more of aspirin produces a rapid clinical antithrombotic effect caused by immediate and near total inhibition of thromboxane A_2 production. (**Moncada S et al., 1979).**

Despite the fact that aspirin has been better studied than any other drug we use in cardiology and despite the fact that it's been around for 105 years, the aspirin resistance is a new story. ***(Deepak L. Bhatt, 2003)***. In a biochemical sense, Aspirin resistance refers to patients who are taking aspirin but do not display an adequate degree of platelet inhibition. **(Califf RM et al., 2002).**

The interest in the concept of aspirin resistance is incredibly high in the whole cardiovascular group, including stroke specialists. So there are a lot of people who talk about aspirin resistance or aspirin non-responders, but there's never been a large-scale clinical trial that has proved that any specific device can measure responsiveness to aspirin and then correlate that with a worse clinical outcome. **(Steven R Steinhubl 2003).**

Using patients who were taking aspirin from the Heart Outcomes Prevention Evaluation (HOPE) study, Eikelboom et al. measured baseline urinary 11-dehydro thromboxane B2 levels, which serve as a marker of thromboxane generation. Levels were compared between those patients taking aspirin who sustained an ischemic event versus those who did not

sustain an event. Those in the highest quartile of urinary thromboxane generation had twice the risk of a myocardial infarction than those in the lowest quartile. ***(Eikelboom JW et al., 2002)***

Investigators from the Cleveland Clinic Foundation performed a prospective, blinded analysis of patients who were aspirin resistant as determined by optical platelet aggregometry, the gold standard for determining Aspirin response. Of the 326 patients with stable cardiovascular disease who were followed, 17 (5.2%) patients were identified as aspirin-resistant and were found to have a three-fold risk for death, myocardial infarction, or stroke compared with the patients who were not deemed aspirin resistant. **(Gum PA et al., 2003)**.

Mild elevations in Creatine kinase MB fraction (myonecrosis) are common after successful percutaneous coronary interventions and are associated with future adverse cardiac events. It occurs in 10% to 40% of the cases. **Abdelmeguid et al** reported that even low-level elevations of CK (1 to 2x upper limit of normal with positive MB fraction) were associated with an increased risk of death over a mean follow-up of 3 years. Some attributing it to the deleterious consequences of myonecrosis on left ventricular function or electrophysiologic stability; others attribute it to the association between risk of CK-MB elevation and coronary atheroma burden. **(Mehran et al., 2000).**

Aspirin resistance as measured by point-of-care assay was showed to significantly increase risk of myonecrosis in patients undergoing PCI as proved by Dr Wai-Hong Chen and

colleagues (Queen Mary Hospital, Hong Kong) **Chen et al's** study thus looked at 151 patients who had been taking aspirin for at least one week before undergoing PCI, who also received a 300-mg loading dose of clopidogrel more than 12 hours before their procedure and a 75-mg maintenance dose on the morning of their procedure. Twenty-nine patients (19.2%) were aspirin resistant, according to a bedside assay. Among these patients, CK-MB elevation was double that of non-aspirin-resistant patients.

In this study, efforts were exerted to detect the actual size of the aspirin resistance problem among Egyptian patients with ischemic heart disease undergoing elective PCI and its impact on myonecrosis, angiographic and clinical outcomes.

Aim of the work

1) To detect the Incidence of aspirin resistance among patients with ischemic heart disease undergoing elective PCI.

2) To study the effect of aspirin resistance on the incidence of myonecrosis after elective PCI.

3) To compare between angiographic outcomes regarding TIMI flow and myocardial blush grading in aspirin responder and aspirin resistant patients.

4) To study clinical outcomes in both groups such as the incidence of in hospital, one month and twelve months MACE {Death, re-infarction, target vessel revascularization (TVR), cerebrovascular stroke, and chronic stable angina Canadian functional class III &IV}.

Patients and methods

Patients:

This study was conducted on 100 patients with chronic stable angina. The patients were recruited from consecutive patients presenting to the outpatient clinic for elective PCI in Ain Shams University hospitals in the period from February 2005 till June 2006.

Inclusion criteria:

1) Patients with proved ischemic heart disease, defined by previous documented coronary stenosis on cardiac catheterization, previous history of myocardial infarction, or previous invasive cardiovascular revascularization procedure.
2) Patients with history of myocardial infarction (more than 3 weeks) who either received or not thrombolytic therapy.
3) Patients with angiographic evidence of > 70% stenosis of the culprit lesion & suitable for PCI.
4) Patients receiving aspirin regularly for at least one week before PCI in a dose 150 mg once daily, compliance on aspirin was determined by patients interview at study enrollment and during follow-up period.

Exclusion criteria:

1) Failure to cross the lesion with the guidewire.
2) Preprocedural elevation of creatine kinase-myocardial band (CK-MB).
3) Preprocedure use of glycoprotein IIb/IIIa inhibitors.
4) The use of non steroidal anti-inflammatory drugs (NSAIDs) or dipyridamole within two weeks before the procedure.

5) Administration of Clopidogrel or Ticlopidine before collecting blood sample to test aspirin resistance.
6) Administration of heparin or low-molecular-weight heparin within 24 hours before enrollment.
7) Patients with platelet count less than 150 000/mm^3.
8) Patients with hemoglobin less than 8gm/dl.
9) Post CABG patients.
10) Major surgical procedure within one week before enrollment.
11) Multi-vessel PCI.

Methods:

All patients was subjected to the following:

1) Full **history** taking including
   - Cardiovascular risk factors e.g. smoking, dyslipidemia, hypertension, diabetes mellitus, positive family history of premature atherosclerosis.
   - Previous Cardiac events.
   - Previous manifestation of atherothrombosis (peripheral vascular disease, cerebrovascular accidents).
   - Detailed history of medical treatment.

2) Full **physical examination** including Body mass index.
BMI was calculated as the weight in kilograms divided by the square of height in meters.

3) Twelve lead **ECG**.

4) **Echocardiography.**
Using General Electric (GE) **Vivid 5** Vingmed technology echocardiography machine. Echocardiography was performed at the initial enrollment and repeated during the follow up period if the patient had any cardiovascular event. Echocadiographic evaluation included: left ventricular dimensions, systolic and diastolic functions, accurate assessment of resting wall motion abnormalities in 16

segments of the LV, left atrial size, proper evaluation of cardiac valves and evaluation of right sided structures and pulmonary artery pressure.

5) Checking the routine lab.

Pre-catheterization routine labs included:

a) Complete blood count (CBC).
b) PT, INR.
c) Serum creatinine.
d) Hepatitis markers.

6) Collecting baseline **blood sample** for CK-MB few hours before the procedure.

The CK-MB is considered elevated if ≥24mg/dl, patients with elevated baseline CK-MB were excluded.

After the procedure by (8-12) hours another blood sample for CK-MB was taken. Post procedural CK-MB was further subdivided into 1 to 3 times the upper limit of normal (up to 72 mg/dl), 3 to 5 times upper limit of normal (72-120 mg/dl), and >5 times upper limit of normal (>120 mg/dl) normal.

Myonecrosis was defined if the post procedure CK MB is ≥3 times the upper limit of normal (ULN).

7) Collecting blood sample for aspirin responsiveness 48 hours before the procedure before receiving an oral loading dose of 300 mg clopidogrel which was taken 12 to 24 hours before the procedure.

Aspirin responsiveness was determined by optical aggregometry test:

Sample:

4.5 ml blood plus 0.5 ml citrate (the withdrawn sample and the test tube should be made of plastic), and the test was performed within 2 hours from withdrawal of the sample.

Reagents:

ADP

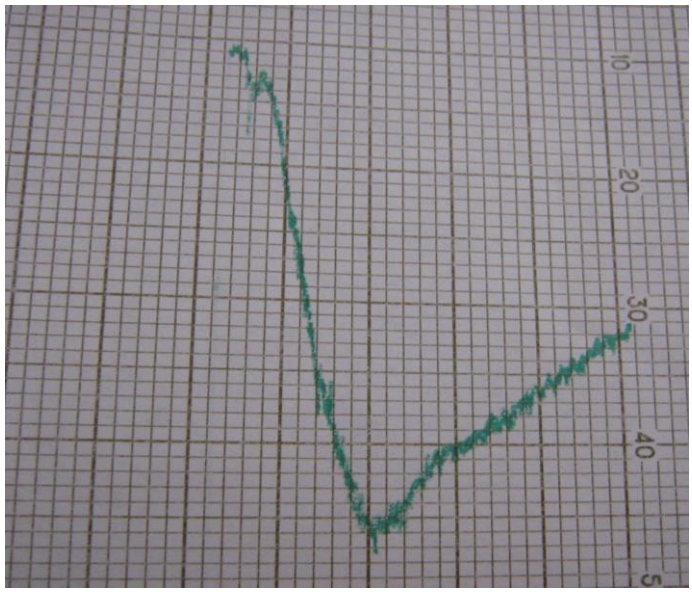
Technique:

1- Centrifuge blood at 800 RPM for 10 minutes.
2- Take platelet rich plasma (PRP) into another tube.
3- Measure PRP on the coulter & should be from 150-300,000 plat/mm3 to continue the procedure.
4- Centrifuge blood again at 3000 RPM for 10 minutes to get platelet poor plasma (PPP).
5- Put PPP as blank in the specific tube.
6- Use two specific tubes for PRP.
7- Open the instrument to warm up 37°C.
8- Put the pen in its place, put both blank tube (PPP) and test tube (PRP).
9- Set baseline and press chart to move the paper.
10- Add 50 ml ADP (10µ).

Determine percentage of aggregation by counting the number of large squares (no. x 10) and divide it on 80.

Figure 28. Optical platelet aggremometer used in this study.

A:



B:

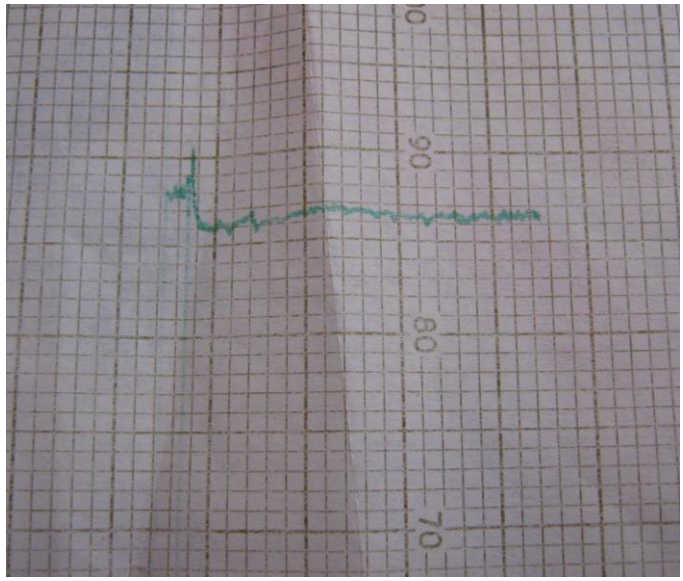


Figure 29. Optical platelet aggregometry results in two patients.
A. platelet aggregation =46% (aspirin responder). Patient no.68
B. platelet aggregation =86% (aspirin resistant). Patient no. 35.

8) **PCI procedure:**

- The procedure was performed according to standard practice, after the patients received an additional 75 mg maintenance dose of clopidogrel.
- Unfractionated heparin 70 U/kg was used for procedural anticoagulation.
- All patients underwent single bare metal stent deployment.
- Direct stenting protocol and pre-dilatation were included.

Angiographic data were collected including:

Lesion location, Reference vessel diameter, severity of the culprit lesion, AHA/ACC classification of the lesion, presence of thrombus and the presence of multi-vessel involvement.

AHA/ACC classification of the lesion:

Type A (low risk):

- Discrete (<10 mm length).
- Concentric
- Readily accessible.
- Non angulated.
- Smooth contour.
- Little or no calcification.
- Less than total occlusion.
- Non ostial.
- No major branch involvement.
- Absence of thrombus.

Type B (moderate risk):

- Tubular (10-20 mm in length).
- Eccentric.
- Moderate tortuosity.
- Irregular contour.
- Some thrombus present.
- Ostial lesion.
- Bifurcational lesion.
- Moderate angulations.
- Moderate /heavy calcification
- Total occlusion < 3 months.

Type C (high risk):

- Diffuse > 2 cm.
- Excessive tortuosity.
- Total occlusion> 3 months
- Degenerated vein graft.
- Extreme angulations.
- Inability to protect major branch.

Angiographic assessment of reperfusion:

A) TIMI Flow grade, grading system for epicardial coronary flow:

- Grade 0: **No perfusion**; no antegrade flow beyond the point of occlusion.
- Grade 1: **Penetration without perfusion**; the contrast material passes beyond the area of obstruction but "hangs up" and fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine run.
- Grade 2: **Partial reperfusion**; the contrast material passes across the obstruction and opacifies the coronary bed distal to the obstruction. However, the rate of entry of contrast into the vessel distal to the obstruction and/or its rate of clearance from the distal bed is perceptibly slower than its entry into and/or clearance from comparable areas not perfused by the culprit vessel (e.g., the opposite coronary artery or coronary bed proximal to the obstruction.
- Grade 3: **Complete perfusion**; antegrade flow into the bed distal to the obstruction occurs as promptly as into the bed proximal to the obstruction and clearance of contrast material from the involved bed is as rapid as from an uninvolved bed in the same vessel or the opposite artery. ***(The TIMI Study Group., 1985)***

B) Myocardial Perfusion Grade:

Grade 0: Dye fails to enter the microvasculature; there is either minimal or no ground glass appearance "blush" in the distribution of the culprit artery indicating lack of tissue level perfusion.

Grade I: Dye slowly enters but fails to exit the microvasculature; there is the ground glass appearance "blush" in the distribution of the culprit lesion that fails to clear from the microvasculature, and dye staining is present on the next injection (approximately 30 seconds between injections).

Grade II: Delayed entry and exit of dye from the microvasculature; there is the ground glass appearance ("blush") in the distribution of the culprit lesion that is strongly persistent at the end of the washout phase (i.e., dye is strongly persistent after 3 cardiac cycles of the washout phase and either does not diminish or only minimally diminishes in intensity during washout).

Grade III: Normal entry and exit of dye from the microvasculature; there is the ground glass appearance ("blush") in the distribution of the culprit lesion that clears normally, and it is either gone or only mildly/moderately persistent at the end of the washout phase (ie, dye is gone or is mildly/moderately persistent after 3 cardiac cycles of the washout phase and noticeably diminishes in intensity during the washout phase), similar to that in an uninvolved artery. ***(The TIMI Study Group.. 1985)***

C) Other angiographic data collected:

- Residual thrombus.
- Transient vessel closure.
- Transient or persistent side branch closure.
- Distal embolization.

All patients were discharged on aspirin 150 mg once daily together with clopidogrel 75 mg once daily for one month, afterwards clopidogrel was stopped and patients were kept on aspirin.

9) **Clinical Follow up:**
we studied the clinical outcomes that included the incidence of in-hospital, one month and twelve months major adverse cardiac event (MACE) including death, re-infarction, target vessel revascularization, cerebrovascular stroke, TIA and angina.

Data management

Data were collected, revised, verified then edited on P.C. The data were then analyzed statistically using SPSS statistical package version (13).

The following tests were done :

1) X = Mean.
2) SD = standard deviation.
3) T test of independent samples.
4) ANOVA= analysis of variance.
5) r = Pearson's correlation coefficient.
6) X^2 = Chi square test.
7) **Linear regression** analysis was used to find out the relation between dependant variable and other quantitative variables using stepwise technique.
8) **Logistic regression** was used to find out the most important dependant predictors of special dependant variable by using backward likelihood ratio technique.

P value >0.05 insignificant
P value <0.05 significant
P value <0.01 highly significant.
(M. Clinton Miller et al., 1992)

Results

The study included 100 patients with chronic stable angina referred to Ain Shams University Hospitals for elective PCI in the period from February 2005 till June 2006.

All patients were receiving aspirin regularly 150 mg once daily for at least one week before enrollment in the study.

All patients underwent elective percutaneous coronary intervention and stenting in single vessel using single bare metal stent for each lesion.

Patients were subjected to full history taking, physical examination, 12 lead ECG, echocardiography before the procedure.

Samples for platelet aggregation test were withdrawn before loading dose of clopidogrel was taken before the PCI.

At the day of the procedure blood sample for baseline CK-MB was taken and another one was taken 8-12 hours after the procedure.

Angiographic characteristics of the lesions and angiographic markers for successful reperfusion were evaluated.

Clinical outcomes including the incidence of in-hospital, one month and twelve months events were recorded.

The basic demographic and clinical characteristics were as the following:

Study included 83 male and 17 female, mean age of the patients was 54.5 ± 6.8 years.

The study included 73 hypertensive patients 27 normotensive, as regards the glycemic state the patients included 53 diabetic patients (27 NIDDM, 26 IDDM) and 47 non diabetic patients. According to the smoking status the study included 44 current smokers, 27 ex smokers and 29 non smokers.

I- Prevalence of aspirin resistance

Platelet aggregation test (**optical aggregometry**) was the test done to evaluate the responsiveness of the patients to aspirin as an antiplatelet agent. Aspirin resistance was defined if platelet aggregation was ≥70% using ADP reagent as was done in the work of Gum PA et al.

Patients were divided into 2 groups according to aspirin responsiveness using optical platelet aggregometry test.

Group 1: Aspirin responders included 88 patients with platelet aggregometry <70%.

Group 2: Aspirin resistant included 12 patients with platelet aggregometry ≥70%.

The prevalence of aspirin resistance among population of the study was 12%.

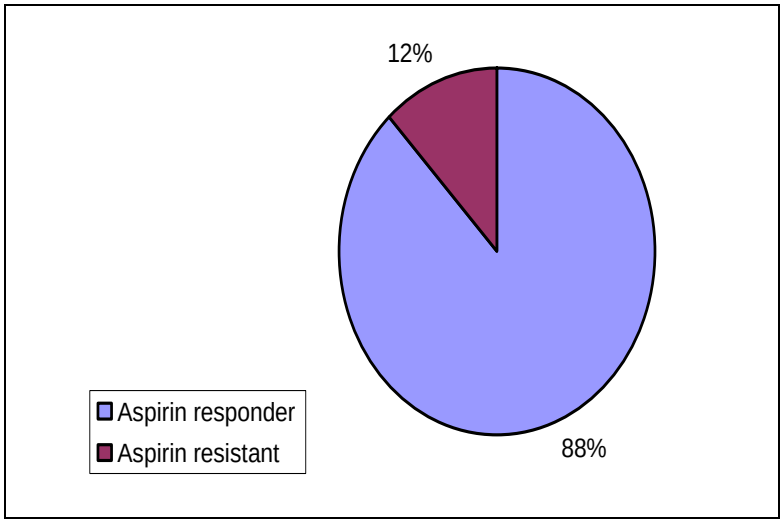


Figure30. showing the incidence of aspirin resistance 12%.

II- Clinical predictors of aspirin resistance

Table 3. Clinical predictors in both groups

	Aspirin responder No. = 88	Aspirin resistant No. = 12	P value
Mean age	51.5 years	59 years	<0.05 significant
Male Gender	83%	83.3%	>0.05 non significant
Mean BMI	27.6 kg/m²	30 kg/m²	<0.05 significant
Hypertension	74%	67%	>0.05 non significant
Current smoker	39%	83.3%	<0.05 significant
DM	50%	75%	<0.05 significant
Dyslipidemia	58%	83%	<0.05 significant
Positive Family history	39%	42%	>0.05 non significant

1) Age and aspirin responsiveness:

Table 4. The mean age in both groups

	Aspirin responders No. = 88	Aspirin resistant No. 12
Mean	51.5 years	59 years
SD	±8.3 years	± 6.2 years
T	3.184	
Significance	< 0.05 (significant)	

In the aspirin responder group the mean age was 51.5 years, with SD ± 8.3 years, while in aspirin resistant group the mean age was 59 ± 6.2 years.

The aspirin resistant patients were significantly older than aspirin responders.

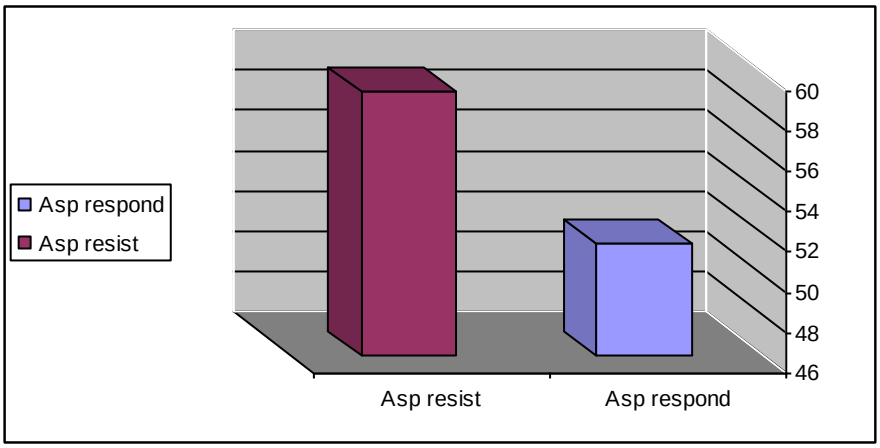


Figure31. Aspirin resistant patients were older than aspirin responders.

2) Gender and aspirin responsiveness:

The study included 83 male and 17 female.

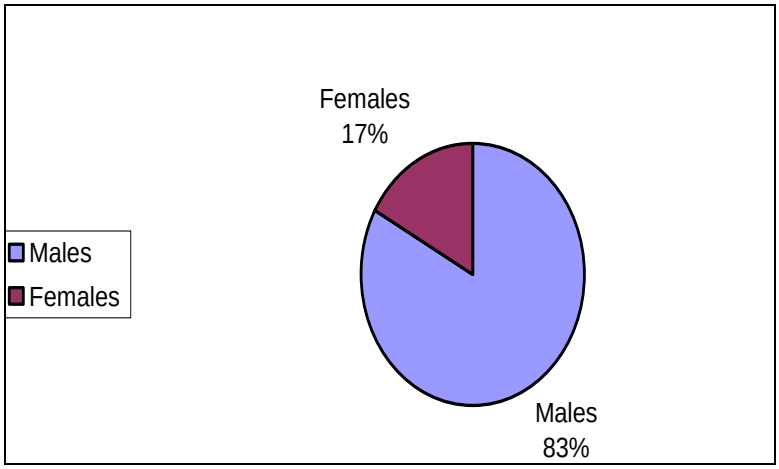


Figure 32. Distribution of gender among patients of the study

Table 5. Gender distribution among both groups.

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	%	no	%
Male	73	83	10	83.3
Female	15	17	2	16.7
X^2	0.001			
Significance	> 0.05 (non significant)			

Group I (aspirin responder) were 88 patients, it included 73 (83%) male patients and 15 (17%) female patients, while Group II (Aspirin resistant) included 12 patients, 10 (83.3%) male patients and 2 (16.7%) female patients.

There was no significant difference between both groups as regards the gender.

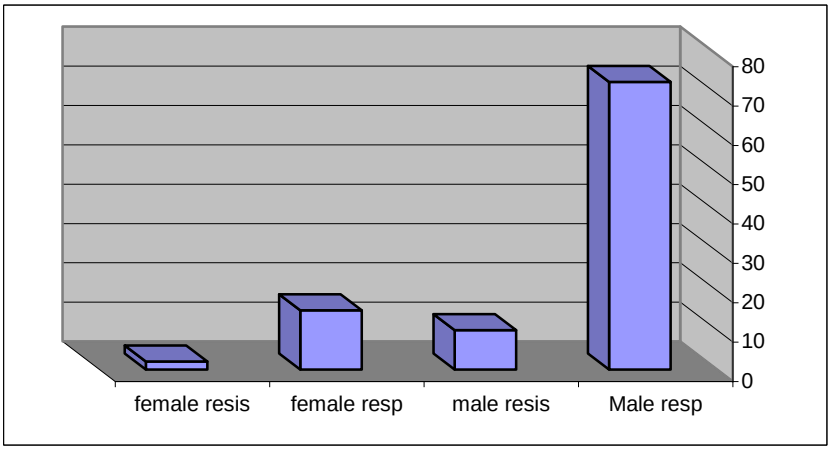


Figure 33. Gender distribution in both groups

3) BMI and aspirin responsiveness:

Table 6. BMI in both groups.

	Aspirin responders No. = 88	**Aspirin resistant No. 12**
Mean	27.6 kg/m²	30 kg/m²
SD	±2.9 kg/m²	± 1.9 kg/m²
T	3.048	
Significance	< 0.05 (significant)	

In the aspirin responder group the mean BMI was 27.6 kg/m² with SD ± 2.9 kg/m², while in aspirin resistant group the mean BMI was 30 kg/m² ± 1.9 kg/m².

The aspirin resistant patients had significantly higher BMI.

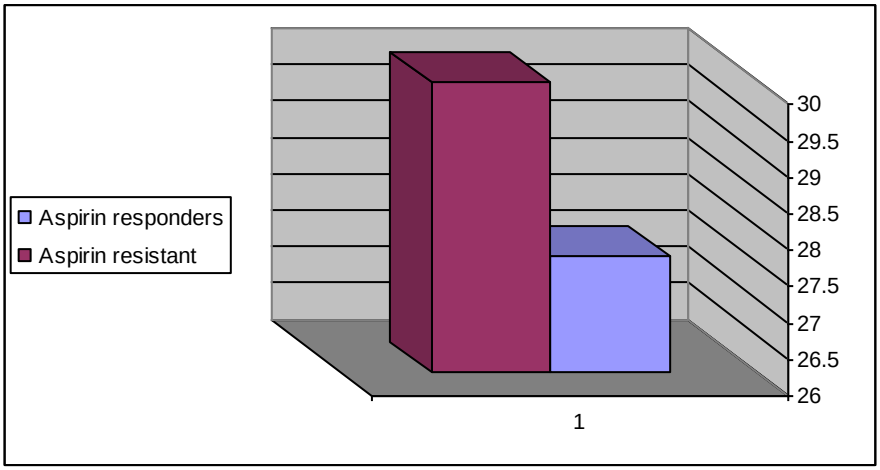


Figure 34. The BMI was higher in aspirin resistant patients

4) Hypertension and aspirin responsiveness:

Table 7. History of hypertension in both groups

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	%	no	%
Hypertensive	65	74	8	67
No history of hypertension	23	26	4	33
X^2	0.278			
Significance	> 0.05 (non significant)			

Aspirin responders group included 65 (74%) hypertensive patients and 23 (26%) patients with no history of hypertension, while in aspirin resistant group, 8 (67%) were hypertensive patients and 4 (33%) patients had no history of hypertension.
There was no significant difference between both groups as regards hypertension.

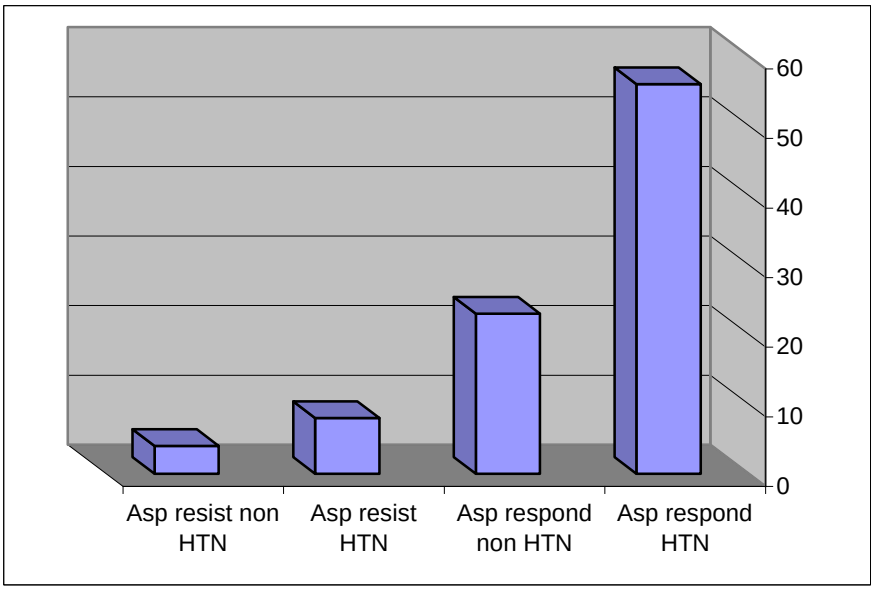


Figure 35. The Hypertension distribution in both groups

5) Smoking and aspirin responsiveness:

Table 8. The smoking status among both groups

	Aspirin responders No. = 88		Aspirin resistant No. 12	
	no	%	no	%
Current smoker	34	39	10	83.4
Non smoker	28	32	1	8.3
Ex smoker	26	29	1	8.3
X^2	1.020			
Significance	< 0.05 (significant)			

Aspirin responders group included 34 (39%) current smokers, 28 (32%) non smokers and 26 (29%) ex smokers, while in aspirin resistant group 10 (83.3%) were smokers, 1 (8.3%) was non smoker and 1 was (8.3%) ex smoker.

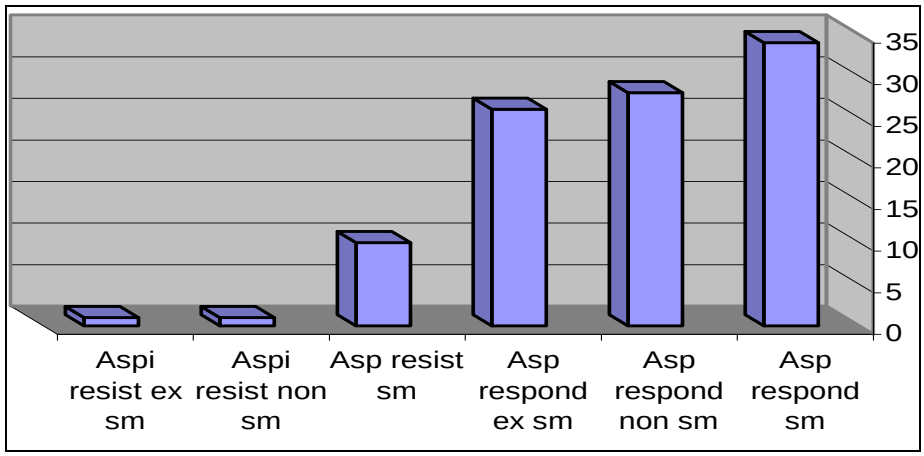


Figure 36. Smoking status distribution in both groups

Most patients in aspirin resistant group were current smokers.

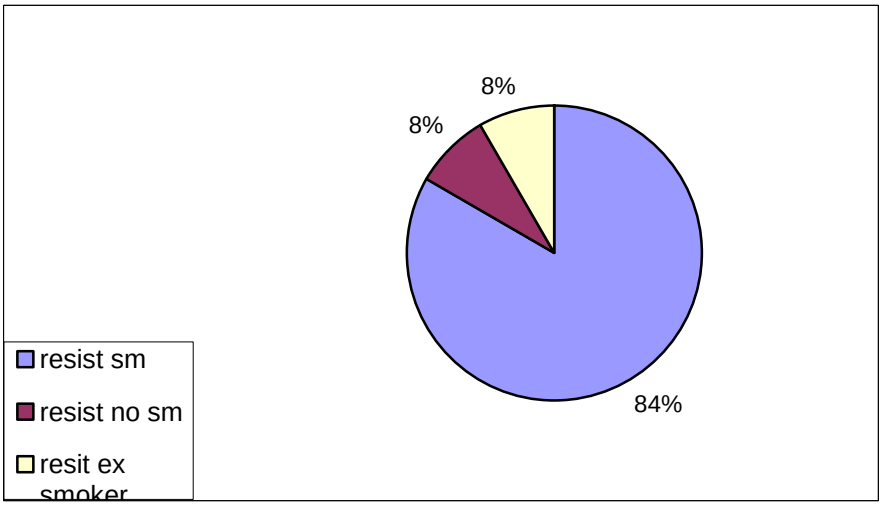


Figure 37. Smoking status in aspirin resistant group.

In current smoker patients (44 patients), the prevalence of aspirin resistance was **23**%, it was almost double the prevalence in the whole patients.

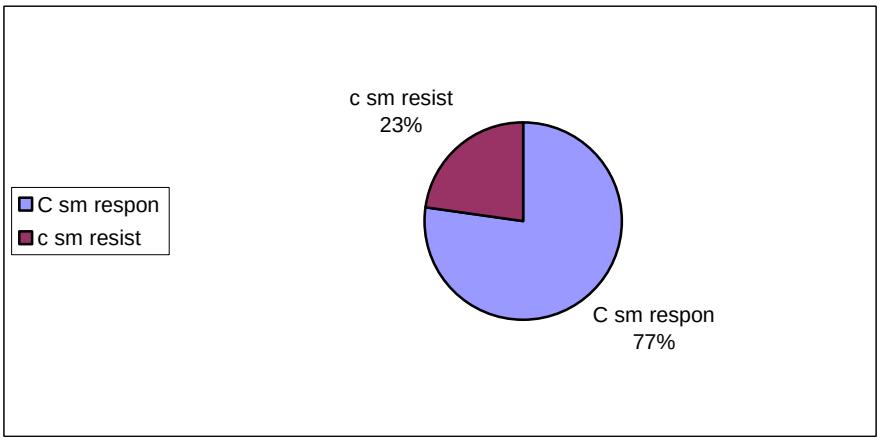


Figure 38. Aspirin response in current smokers.

6) History of DM and aspirin responsiveness:

The study included 53 diabetic patients (27 NIDDM and 26 IDDM) and 47 non diabetic patients.

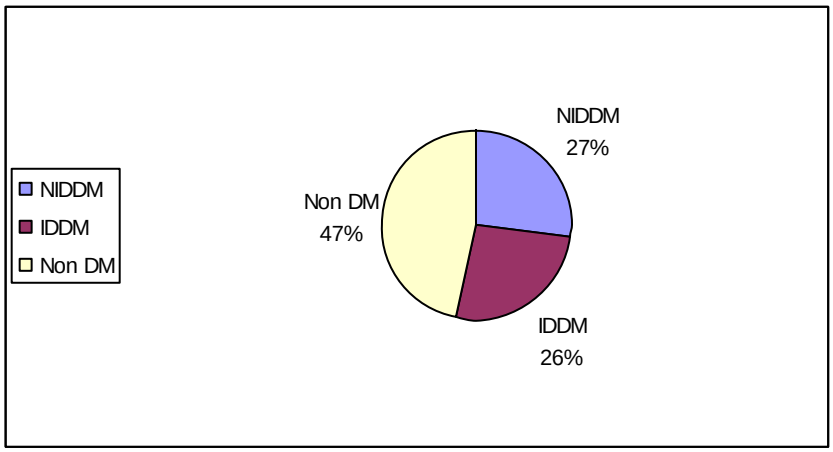


Figure39. Distribution of DM among patients included in the study.

Table 9. The history of DM among both groups

	Aspirin responders No. = 88		Aspirin resistant No. 12	
	no	%	no	%
NIDDM	25	28	2	17
IDDM	19	22	7	58
Non DM	44	50	3	25
X^2	7.538			
Significance	< 0.05 (significant)			

Aspirin responders group included 25 (28%) NIDDM patients, 19 (22%) IDDM patients and 44 (50%) non diabetic patients, while in aspirin resistant group 2 (17%) patients were NIDDM, 7 (58%) patients were IDDM, 3 (25%) patients were non diabetic.

Aspirin resistance was significantly more common among diabetic patients especially IDDM patients.

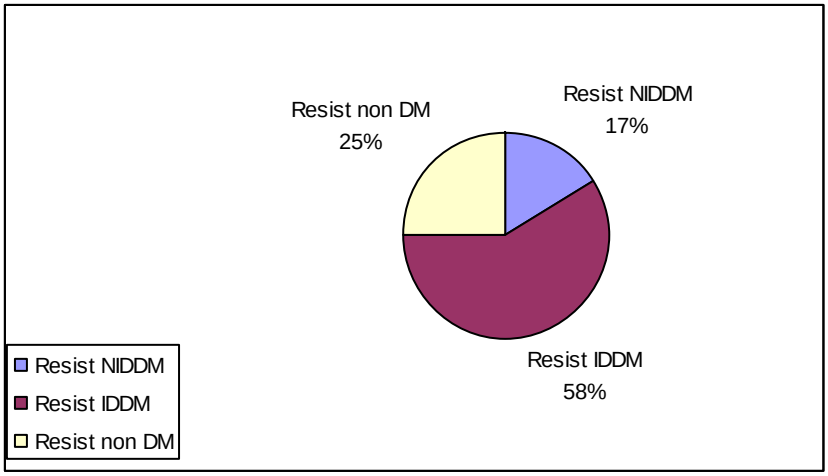


Figure 40. History of DM among aspirin resistant group

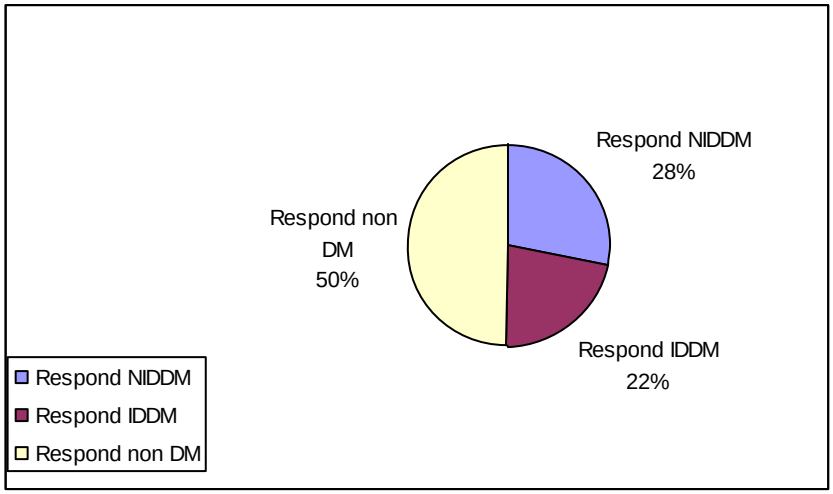


Figure 41. History of DM among aspirin responder group

Among diabetic patients (53), nine patients (17%) were aspirin resistant, so the **prevalence of aspirin resistance in diabetic patients was 17%**.

Among diabetic patients, IDDM patients were 26, of them 9 patients were aspirin resistant, so the **prevalence of aspirin resistance among IDDM was 27%.**

NIDDM patients were 27 patients, only two patients were aspirin resistant, so the **prevalence of aspirin resistance among NIDDM patients was 7%**.

While in non diabetic patients (47), only three patients were aspirin resistant, so the **prevalence of aspirin resistance among non diabetic patients was 6%** only.

In this study aspirin resistance was more prevalent among patients with IDDM.

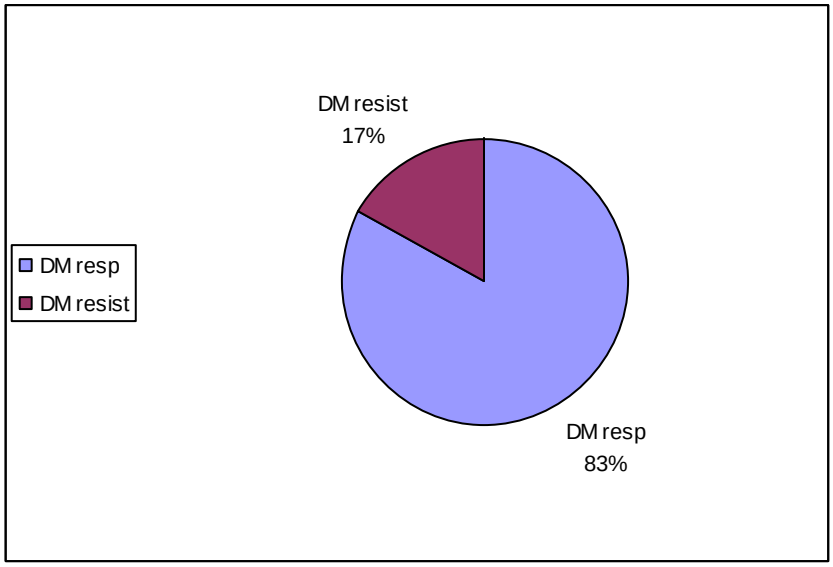


Figure 42. Aspirin responsiveness among diabetic patients

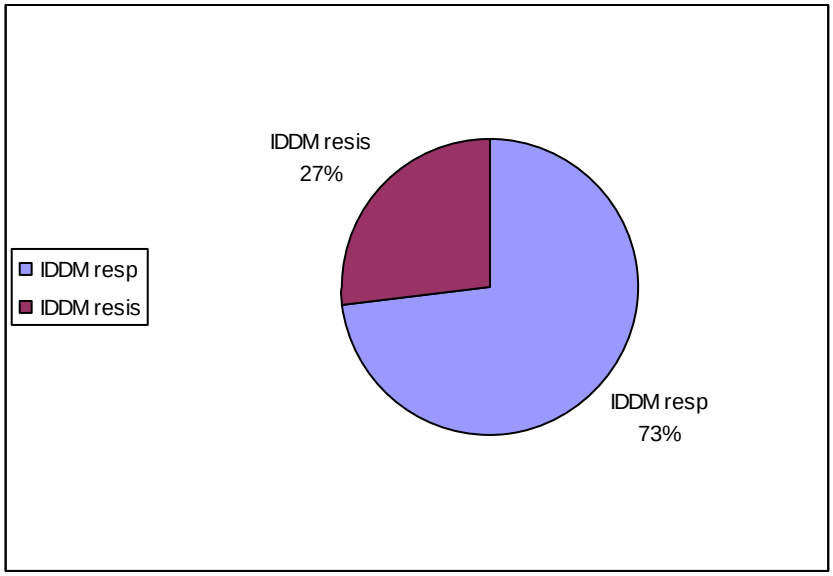


Figure 43. Aspirin responsiveness among IDDM patients

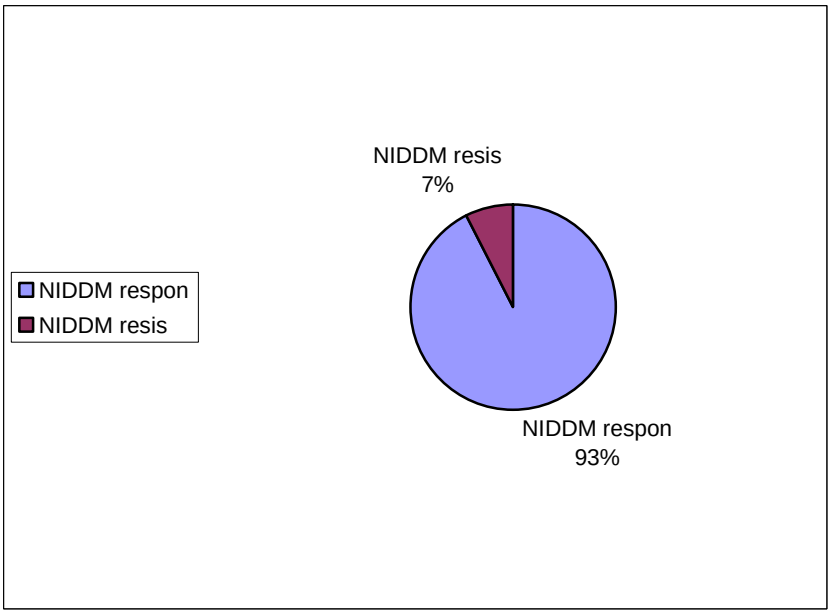


Figure 44. Aspirin responsiveness among NIDDM patients

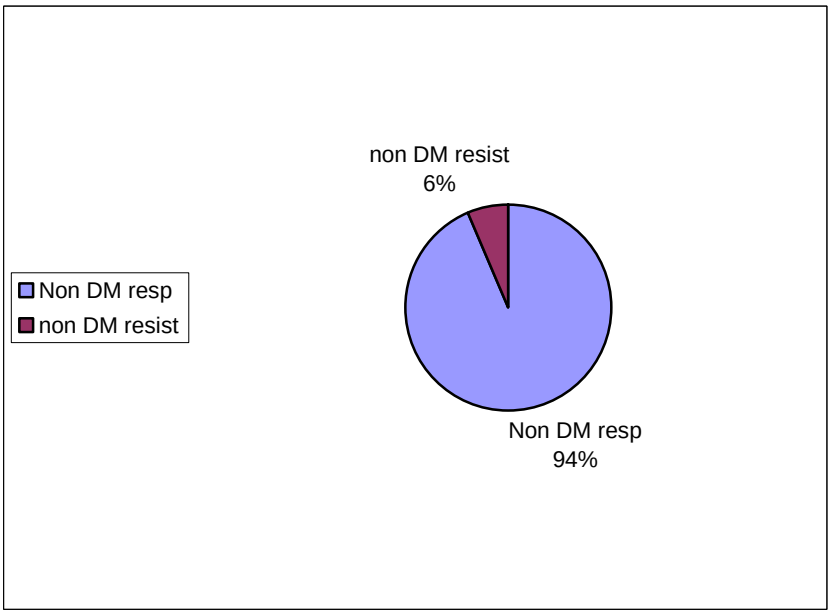


Figure 45. Aspirin responsiveness among non diabetic patients

7) Dyslipidemia and aspirin responsiveness:

Table 10. History of dyslipidemia among both groups.

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	%	no	%
Dyslipidemic	51	58	10	83
No history of dyslipidemia	37	42	2	17
X^2	0.716			
Significance	< 0.05 (significant)			

Aspirin responders group included 51 (58%) dyslipidemic patients and 37 (42%) patients had no history of dyslipidemia, while in aspirin resistant group 10 (83%) patients were dyslipidemic with 2 (17%) patients had no history of dyslipidemia.

Aspirin resistance was significantly more common among dyslipidemic patients.

The study included 61 dyslipidemic patients, in these patients 10 were aspirin resistant patients. **The prevalence of aspirin resistance among dyslipidemic was 16%.**

In 39 patients included in the study with no history of dyslipidemia, 2 patients were aspirin resistant patient. **The prevalence in patient with no history of dyslipidemia was** 5%.

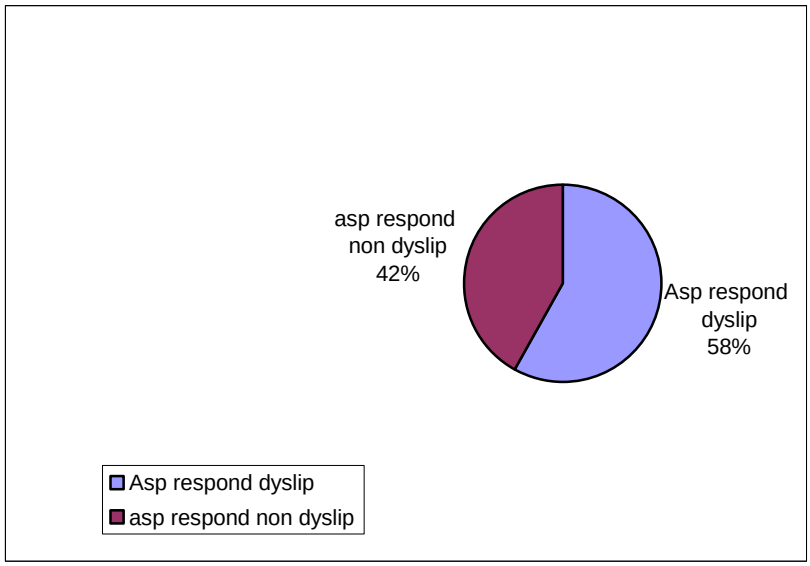


Figure 46. Dyslipidemia among aspirin responder group

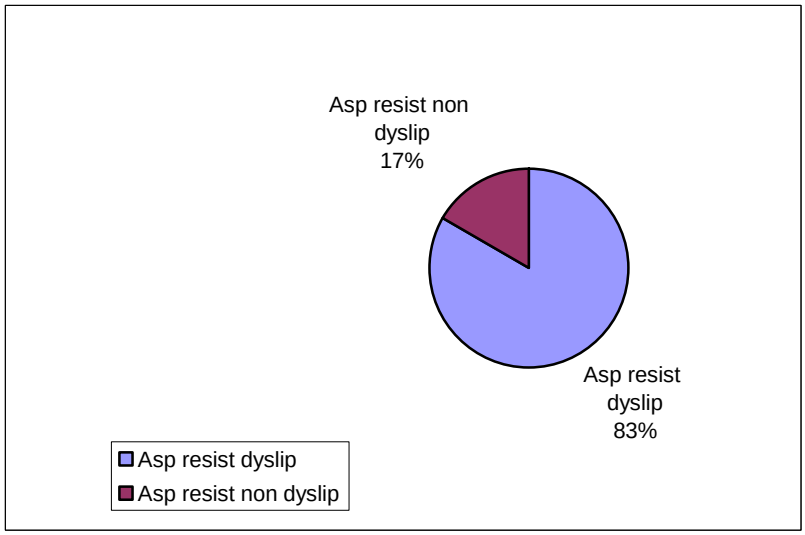


Figure 47. Dyslipidemia among aspirin resistant group

8) Family history of premature atherosclerosis and aspirin responsiveness

Table 11. Family history among both groups.

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	%	no	%
Positive	34	39	5	42
Negative	54	61	7	58
X^2	0.041			
Significance	> 0.05 (non significant)			

Aspirin responders group included 34 (39%) patients with positive family history of premature atherosclerosis and 54 (61%) patients with negative family history, while in aspirin resistant group 5 (42%) patients had positive family history and 7 (58%) patients had negative family history.

There was no significant difference between both groups as regards family history of premature atherosclerosis.

III- Laboratory predictors of aspirin resistance

Table 12. Laboratory predictors of aspirin resistance

	Aspirin responder No. = 88	**Aspirin resistant No. = 12**	**P value**
Mean S. creatinine	1.1 mg/dl	1.5 mg/dl	<0.001 highly significant
Mean platelet count	268000/mm³	258000/ mm³	>0.05 non significant

1) Serum creatinine and aspirin responsiveness:

the study included 88 patients who had baseline s. creatinine less than 1.5 mg/dl, 12 patients had renal impairment with baseline Serum creatinine > 1.5 mg/dl.

In the aspirin resistant group (12 patients), 6 (50%) patients had serum creatinine > 1.5 mg/dl, while in aspirin responders (88 patients), 6 (7%) patients had serum creatinine greater than 1.5 mg/dl.

Renal impairment was significantly more common among aspirin resistant patients.

Table 13. Mean S Creatinine in both groups.

	Aspirin responders No. = 88	**Aspirin resistant No. 12**
Mean	1.1 mg/dl	1.5 mg/dl
SD	±0.34 mg/dl	± 0.1 mg/dl
T	4.363	
Significance	< 0.001 (highly significant)	

In the aspirin responder group the mean s. creatinine was 1.1 mg/dl, with SD ± 0.34 mg/dl, while in aspirin resistant group mean s. creatinine was 1.5 mg/dl, ± 0.1 mg/dl.

Aspirin resistance was associated with higher S. creatinine.

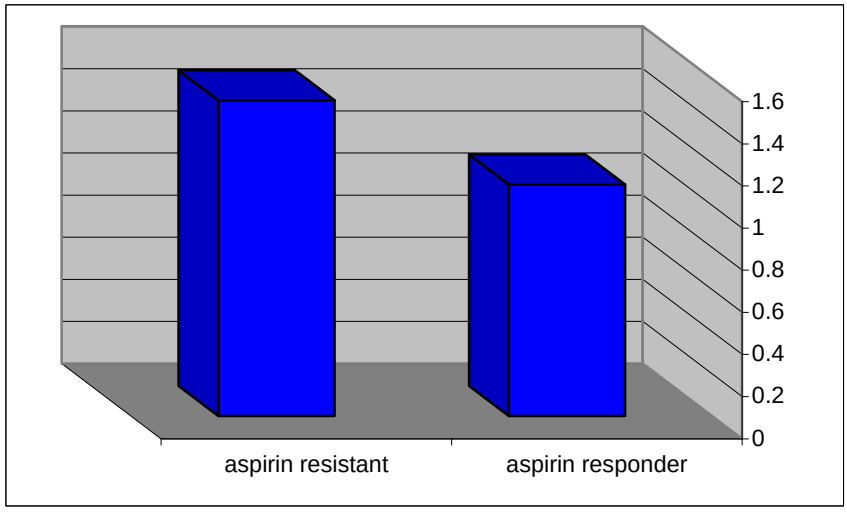


Figure 48. Mean s. creatinine among both groups

This study included 12 patients with chronic renal impairment, among these patients 6 patients had aspirin resistance. **The prevalence of aspirin resistance among patients with chronic renal impairment included in this study was 50%.** While in patients with normal baseline serum creatinine (88) patients, 6 patients had aspirin resistance, so the **prevalence of aspirin resistance among patients with normal baseline serum creatinine included in the study was 7%.**

There was a statistically significant positive correlation between serum creatinine and platelet aggregation, the higher serum creatinine the less platelet inhibition by aspirin using Pearson's correlation coeffiencient. (R value = 0.668)

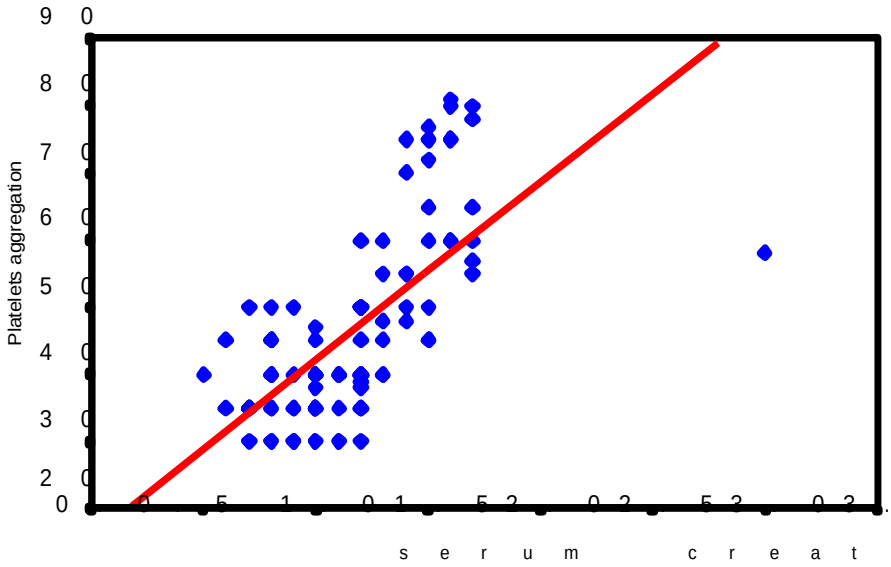


Figure 49. Correlation between s. creatinine and platelet aggregation. R value=0.668

2) Platelet count and aspirin responsiveness:

Table 14. The mean platelet count in both groups.

	Aspirin responders No. = 88	**Aspirin resistant No. 12**
Mean	268000/mm³	258000/mm³
SD	±67000/mm³	± 68000/mm³
T	0.630	
Significance	> 0.05 (non significant)	

In the aspirin responder group the mean platelet count was 268000/mm³, with SD ± 67000/mm³, while in aspirin resistant group mean platelet count was 258000/mm³ ± 68000/mm³.
There was no significant difference between both groups as regards platelet count.

IV- Angiographic predictors of aspirin resistance

Table 15. Angiographic predictors of aspirin resistance

	Aspirin responder No. = 88	**Aspirin resistant No. = 12**	**P value**
Mean RVD	3.03 mm	2.9 mm	>0.05 non significant
Mean severity of the culprit lesion	89%	92%	>0.05 non significant
Presence of MVD	11%	50%	< 0.05 significant
Thrombus containing lesion	1%	2%	>0.05 non significant

1) Lesion location and aspirin responsiveness:

Table 16. Lesion location in both groups.

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	**%**	**no**	**%**
LAD	36	41	6	50
LCx	31	35	3	25
RCA	21	24	3	25
X^2	0.538			
Significance	> 0.05 (non significant)			

In the aspirin responders group 36 (40%) patients had the culprit lesion in the LAD, 31 (35%) patients had the culprit lesion in the LCx and 21 (24%) patients had the culprit lesion in the RCA, while in aspirin resistant group 6 (50%) patients had the culprit lesion in the LAD, 3 (25%) patients had the culprit lesion in the LCx and 3 (25%) patients had the culprit lesion in the RCA.

There was no statistically significant difference between both groups as regards lesion location.

2) Reference vessel diameter and aspirin responsiveness:

Table 17. RVD in both groups.

	Aspirin responders No. = 88	**Aspirin resistant No. 12**
Mean	3.03 mm	2.9 mm
SD	±0.292 mm	± 0.316 mm
T	0.865	
Significance	> 0.05 (non significant)	

In the aspirin responder group the mean RVD was 3.03 mm, with SD ± 0.292 mm, while in aspirin resistant group the mean RVD was 2.9 mm, with SD ± 0.316 mm.

There was no significant difference between both groups as regards RVD.

3) Severity of the culprit lesion and aspirin responsiveness:

Table 18. Lesion severity in both groups

	Aspirin responders No. = 88	**Aspirin resistant No. 12**
Mean	89%	92%
SD	±5%	± 3.3%
T	1.9	
Significance	> 0.05 (non significant)	

In the aspirin responder group the mean percentage of severity of the lesion was 89%, with SD ± 5%, while in aspirin resistant group mean percentage of severity of the lesion was 92% with SD ± 3.3%.

There was no significant difference between both groups as regards mean percentage of severity of the lesion.

4) AHA lesion classification of the culprit lesion and aspirin responsiveness:

Table 19. AHA classification of the culprit lesion in both groups

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	**%**	**no**	**%**
Type A	58	66	7	58
Type B	20	23	3	25
Type C	10	11	2	17
X^2	10.215			
Significance	> 0.05 (non significant)			

In Group I (aspirin responders) culprit lesion with AHA type A in 58 (66%) patients, type B in 20 (23%) patients and type C in 10 (11%) patients while in Group II (aspirin resistant) culprit lesion was AHA type A in 7 (58%) patients, type B in 3 (25%) patients and type C in 2 (17%) patients.

There was no significant difference between both groups as regards AHA classification of the culprit lesion.

5) Presence of multi-vessel disease and aspirin responsiveness:

Table 20. Presence of multi-vessel disease in both groups

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	**%**	**no**	**%**
Single vessel disease	78	89	6	50
Multi-vessel disease	10	11	6	50
X^2	11.729			
Significance	< 0.05 (significant)			

In Group I (aspirin responders) patients had single vessel disease were 78 (89%) patients, multi vessel disease 10 (11%) patients, while in Group II (aspirin resistant) patients had single vessel disease was 6 (50%) patients, multi vessel disease 6 (50%) patients.

Aspirin resistant group was associated with more extensive coronary atherosclerosis.

The study included 16 patients with multi-vessel disease and 84 patients with single vessel disease. In MVD patients, 6 patients were aspirin resistant. The prevalence of aspirin resistance among patients with MVD was 37.5%.

6) Thrombus containing culprit lesion and aspirin responsiveness:

Table 21. The presence of thrombus in the culprit lesion in both groups

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	**%**	**no**	**%**
No thrombus	87	99	11	92
Thrombus containing lesion	1	1	1	8
X^2	2.791			
Significance	>0.05 (non significant)			

In Group I (aspirin responders) culprit lesion was angiographically not containing thrombus in 87 (99%) patients, thrombus containing in 1 (1%) patient, while in Group II (aspirin resistant) culprit lesion was angiographically not containing thrombus in 11 (92%) patients, thrombus containing in 1 (8%) patient.

There was no statistically significant difference between both groups as regards thrombus content in the culprit lesion.

Table 22. Correlation between platelet aggregation versus different quantitative variables by linear regression analysis

Variables	Beta co-efficient	P
S. creatinine	0.53	**<0.01****
Age	0.42	**<0.05****
BMI	0.25	**<0.05****

This table indicates that S. creatinine, age and BMI are positively correlated with platelets aggregation.

Table 23. Correlation between platelet aggregation versus qualitative variables by logistic regression analysis:

Independent predictors	Beta co-efficient	P	Odd's ratio (95%CI)
MVD	1.7	<0.05*	3 (0.9-5.2)
Smoking	1.5	<0.05*	1.5 (0.7-4.3)
DM	1.3	<0.05*	1.4 (0.6-2.9)
Dyslipidemia	1.2	<0.05*	1.3 (0.7-3.2)

This table indicates that presence of MVD, smoking, diabetes mellitus and dyslipidemia (in descending manner) are considered the most important independent predictors for aspirin resistance.

IV- Outcomes according to aspirin responsiveness

1) Myonecrosis

Myonecrosis was defined as post procedure CK MB elevation > 3 ULN.

Table 24. Post procedural CK MB elevation in both groups.

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	%	no	%
> 3 ULN	25	28	12	100
< 3ULN	63	72	0	0
X^2	0.041			
Significance	< 0.001 (highly significant)			

In aspirin responder group 25 (28%) patients had post procedure CK MB elevation > 3 times (myonecrosis), in these patients only one patient (1.1%) had CK MB elevation > 5 times, 63 (72%) patients had CK MB elevation < 3 times (no myonecrosis), while in aspirin resistant group all (100%) patients had post procedure CK MB elevation > 3 times, 8 (66.7%) of them had CK MB elevation > 5 times.

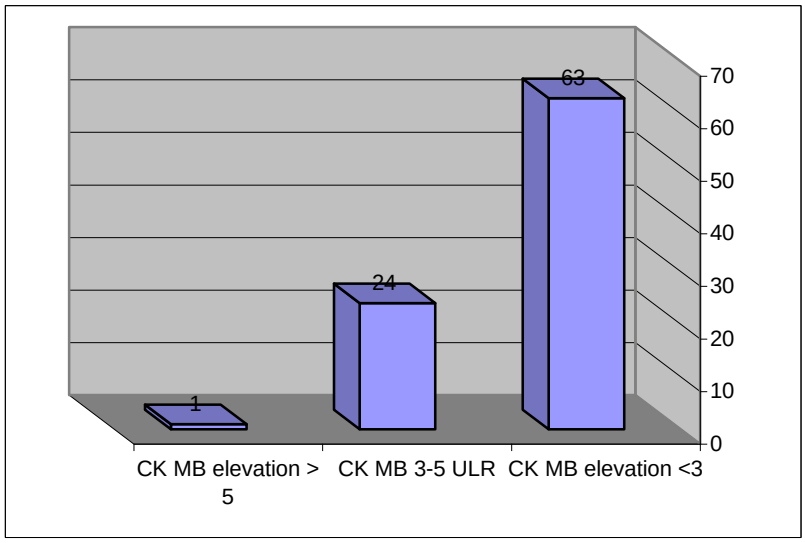


Figure 50. CK MB elevation in aspirin responders

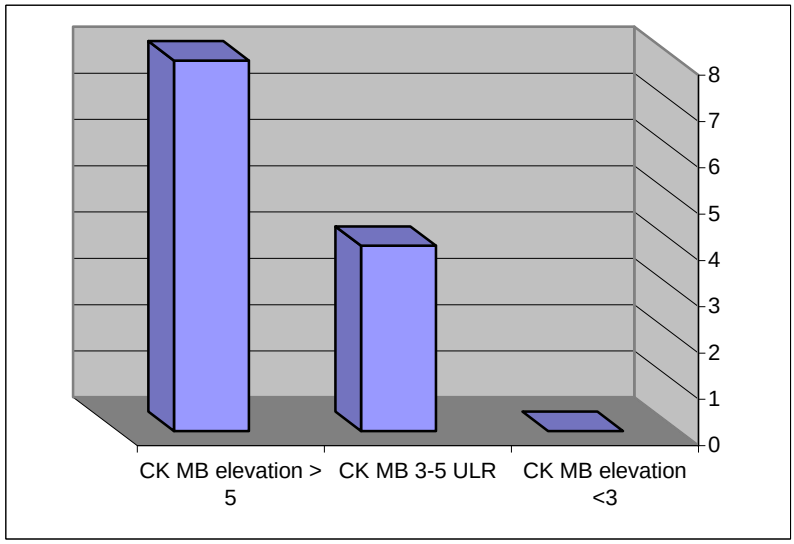


Figure 51. CK MB elevation in aspirin resistant patients

Table 25. Mean CK MB elevation in both groups.

	Aspirin responders No. = 88	Aspirin resistant No. 12
Mean	2.04	4.88
SD	±1.01	± 0.91
T	8.049	
Significance	< 0.001 (highly significant)	

The mean CK MB elevation in aspirin responder group was 2.04 with SD ±1.01, while in aspirin resistant patient the mean CK MB elevation was 4.88 with SD ± 0.91.

Aspirin resistance was associated with statistically significant higher incidence and more severe myonecrosis.

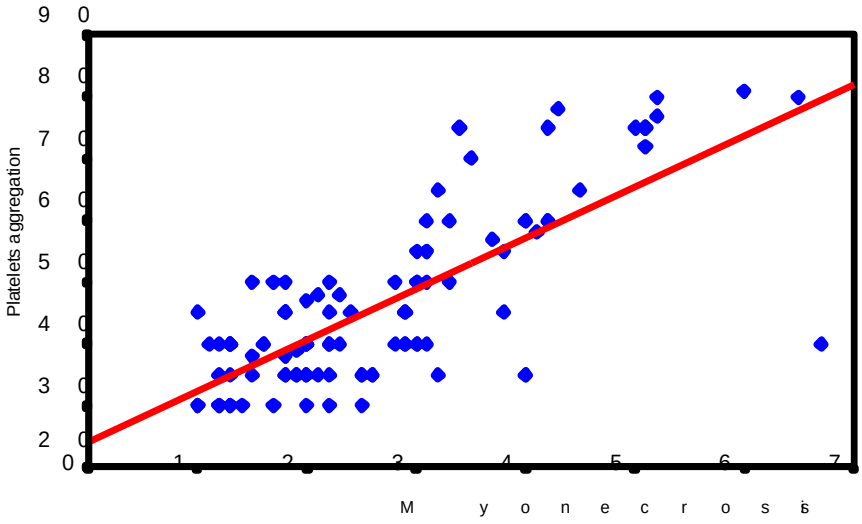


Figure 52. Correlation between myonecrosis and platelet aggregation R value=0.758

There was a highly significant positive correlation between myonecrosis and **platelet aggregation**, the higher the platelet aggregation the more post procedural CK MB rise even without reaching the threshold for the definition of aspirin resistance using Pearson's correlation coefficient. R value= 0.758

2) Angiographic outcome:

A) Post procedure TIMI flow and aspirin responsiveness:

Table 26. TIMI flow in both groups

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	%	no	%
TIMI III flow	86	98	9	75
Less than TIMI III flow	2	2	3	25
X^2	1.020			
Significance	< 0.05 (significant)			

In Aspirin responders 86 (98%) patients had post procedure TIMI III flow, only 2 (2%) patients had post procedure TIMI II flow. In aspirin resistant group TIMI III flow was achieved in 9 (75%) patients while 3 (25%) patients had post procedure TIMI II flow.

Aspirin responders had better post PCI TIMI flow in the culprit lesion.

B) Post procedure MBG and aspirin responsiveness:

Table 27. Post procedural MBG in both groups

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	%	no	%
MBG III	84	95	8	67
Less than MBG III	4	5	4	33
X^2	2.430			
Significance	< 0.05 (significant)			

In Aspirin responders 84 (95%) patients had post procedure MBG 3, only 4 (5%) patients had post procedure MBG 2. In aspirin resistant group 8 (67%) patients had post procedure MBG 3, only 4 (33%) patients had post procedure MBG 2.

Aspirin responders had better post PCI MBG in the territory of the culprit vessel.

There was no use of glycoprotein IIb/IIIa inhibitors in any of the patients; no clinical bleeding events occurred.

3) Clinical Outcomes

Patients in both groups were followed up, mean period of follow up was 12 months ± 2.3 months for death, new Q wave MI, cerebrovascular stroke, TIA and recurrence of chest pain.

In hospital outcomes:

No clinical bleeding events occurred, no death, no Q wave MI, no cerebrovascular stroke. All patients were discharged home on the next day of the procedure.

One months follow up:

In the aspirin responder group, one patient had recurrence of chest pain (chronic stable angina), in the aspirin resistant group also one patient recurrence of chest pain (chronic stable angina).

Twelve months follow up:

Table 28. Twelve months clinical follow up in both groups

	Aspirin responders No. = 88		**Aspirin resistant No. 12**	
	no	**%**	**no**	**%**
Free follow up period	80	90.9	8	66.6
Had event during the follow up period	8	9.1	4	33.3
X^2	8.249			
Significance	<0.05 (significant)			

Follow up of patients in group I (aspirin responders) revealed 80 (90.9%) patients had event free 12 months follow up, 8 (9.1%) patients had events, 6 of these patients had recurrent chest pain (chronic stable angina), two patients had transient ischemic attack (TIA).
In group II (aspirin resistant) 8 (67%) patients had event free 12 months follow up, 4 (33%) patients had events, 2 of them had recurrent chest pain (chronic stable angina), one patient had transient ischemic attack, one patient was admitted to the hospital 50 days after the procedure with unstable angina but he refused to have coronary angiogram performed and was controlled on medical treatment.

During 12 months follow up aspirin resistant patients had significantly higher rates of adverse cardiovascular events than aspirin responders.

So, aspirin resistance was linked with worse clinical outcomes, aspirin resistance was proved to be associated with more severe form of **myonecrosis**, and aspirin resistance was associated with less post procedure **TIMI flow** and less post procedure **MBG**.

Discussion

This study was performed in Ain Shams University to demonstrate the prevalence of aspirin resistance among Egyptian population undergoing elective percutaneous coronary angioplasty.

This study was performed in a prospective fashion. Those performing the optical aggregation testing were blind to clinical histories, and follow-up was done in a blinded manner without regard to aspirin sensitivity.

We prospectively set out to measure the incidence of aspirin resistance in ischemic heart disease population undergoing elective PCI and to determine its impact on myonecrosis, angiographic outcome and clinical follow up.

Laboratory detection of aspirin resistance

We utilized **optical platelet aggregation**, the current gold standard of platelet aggregation to measure aspirin responsiveness. Although the term "aspirin resistance" has not been clearly defined. Aspirin resistance was defined in this study as the failure of aspirin 150 mg/day, given for a minimum of seven days before testing, to suppress agonist-induced platelet aggregation, as measured by optical platelet aggregometry. based on the work of Gum PA et al, if mean aggregation $\geq$ 70% to 10 µmol/L ADP the patient is considered aspirin resistant.

Unlike many other laboratory measures of platelet function, optical platelet aggregometry is widely available and is routinely used to assess platelet function and to measure the antiplatelet effects of aspirin. However, there are various other techniques to measure platelet aggregation, including whole-blood aggregometry, yet it is difficult to assess which

technique is the most accurate and valid measure of aspirin resistance without direct comparisons of their clinical relevance.

Although considered historical gold standard test, the platelet aggregometry has the following disadvantages:

- The test is techniqually demanding and relatively expensive.
- Test is laborintensive and its reproducibility depends on platelet concentration, agonist type and concentration.
- Test should be performed within 2 hours from withdrawal of the sample.

Other laboratory tests for aspirin responsiveness were used in recent trials included:

♦ Measuring **Urinary thromboxane metabolite** (11-dihydroxy thromboxane B2) in one random urine sample was the test used in case-control sub-study from the population of (HOPE) trial, aspirin resistant patients were considered when urinary thromboxane levels> 33.8 ng/mmol creatinine. ***(Eikelboom JW et al., 2002)***, However because the concentration of 11-dehydro thromboxane B2 in the urine reflects both platelet and non platelet sources of thromboxane generation, this may **not** be a specific measure of the antiplatelet effects of aspirin.

♦ More recently **point of care** tests were introduced in the field for simple and rapid use including *Rapid Platelet Function Analyzer (PFA)- 100* that was used by Gum PA et al and *Ultegra Rapid Platelet Function Assay-ASA VerifyNow aspirin system* that was used by Chen et al, when the reading is greater than 550 aspirin reactive units (ARU), as described by the manufacturer, the patient is categorized as being aspirin-resistant.

Rapid Platelet Function Analyzer (PFA)- 100 is increasingly being used in clinical practice to screen for inherited or acquired haemostatic disorders. However, the PFA-100 does

not provide a specific measure of the antiplatelet effects of aspirin and may lack sensitivity for measuring the antiplatelet effects of low-dose aspirin.

♦ Skin ***bleeding time*** has also been used to measure the antiplatelet effects of aspirin but it is a nonspecific measure of platelet function, is operator dependent, and has limited reproducibility.

To have a universal accepted definition for aspirin resistance requires a specific, accurate, and reproducible laboratory measure of the antiplatelet effects of aspirin, the results of which can be generalized to other laboratories and patients. **None of the currently available laboratory tests of the antiplatelet effects of aspirin has yet been demonstrated to meet adequately these criteria**.

Other important factor for detection of aspirin resistance is **timing** of the test as several serial studies of platelet aggregometry suggest that the antiplatelet effects of aspirin vary over time (*Mueller MR et el 1997*), *(Helgason CM et al., 1993*). Other showed persistent lack of responsiveness over the entire follow up period *(Weksler BB et al., 1983*).

In this study aspirin responsiveness was tested **once** at enrollment just as was done in all recent trials for detection of clinical significance of aspirin resistance.

Prevalence of aspirin resistance

Prevalence widely differ between studies reporting on aspirin resistance. Aspirin **dosage**, the **method** of defining aspirin resistance, **type** and **concentration** of the agonist used and **population** of patient selected in the study strongly influence estimated prevalence.

A lot of variability exists in the literature in terms of just how prevalent of aspirin resistance, ranging from **5% to 60%.**

In this study we tested stable patients with established diagnosis of ischemic heart disease referred for elective cardiac catheterization using optical aggregometry test with (ADP) reagent. Patients were kept on aspirin 150 mg/day according to the our standard clinical practice, the incidence of aspirin resistance was 12%.

Buchanan et al studied 40 **post CABG** patients treated with 325 mg of aspirin daily, compared them on aspirin and off aspirin, and found that approximately **42**% of the patients were considered non-responders and had no significant response or no change in **bleeding time.**

Muller et al studied 100 patients with **peripheral vascular disease** with **whole blood aggregation** tests and showed a **60**% incidence of aspirin resistance.

Gum et al studied 325 patients with **stable ischemic heart disease** using **optical platelet aggregometry** showed **5.5**% incidence of aspirin resistance and **23**% were aspirin semi-responders, Using the rapid Platelet Function Analyzer (PFA)-100® **9.5**% were aspirin resistant.

Wai-Hong Chen et al studied **151** patients scheduled for non-urgent PCI, using the Ultegra Rapid Platelet Function Assay-ASA, 29 (19.2%) patients were noted to be aspirin-resistant.

Predictors of aspirin resistance

The association between aspirin resistance and risk factors for atherothrombosis (smoking, hypertension, DM and dyslipidemia) was not adequately studied, initially most trial identifying aspirin resistance had limited number of patients without clinical follow up period, more recent trials (work of Chen et al and Gum et al) had a larger number of patients, longer follow up period and published the clinical, angiographic and procedural characteristics in both aspirin responders and aspirin resistant patients.

Clinical predictors:

I- Age:

In this study, **The aspirin resistant patient were statistically significant older than aspirin responders.** In the aspirin responder group the mean age was 51.5 years, with SD ± 8.3 years, while in aspirin resistant group the mean age was 59 years, with SD ± 6.2 years.

In Chen et al work, aspirin resistant patients was **non** statistically significant older than aspirin responder patients, the mean age in aspirin responders was 63.7 ± 11.8 years, while in aspirin resistant group it was 65.6 ± 9.7 years.

In the work of Gum et al, there was no statistical significant difference in both groups as regard the age, the mean age in aspirin responders was 62 ± 11 years, while in aspirin resistant group it was 59 ± 15 years.

II- Gender:

In this study, **there was no significant difference in both groups as regards the gender**. Aspirin responder were 88 patients, 73 (83%) male and 15 (17%) female, while in Aspirin resistant group 12 patients, 10 (83.3%) were male and 2 (16.7%) female.

In the work of Chen et al, there were statistically significant **higher incidence of female** patients in the aspirin-resistant group 44.8% versus 19.7% in aspirin responders.

In the work of gum et al, there was also **higher incidence of female** patients in the aspirin-resistant group 47% of the aspirin resistant group were female patients while, 21% of the aspirin responder group were female patients.

The difference between our study and other studies may be due to the limited number of female enrolled in the study (17 females).

III- Body mass index:

In this study, **The aspirin resistant patient had significantly higher BMI**. In the aspirin responder group the mean BMI was 27.6 kg/m², with SD ± 2.9 kg/m², while in aspirin resistant group the mean BMI was 30 ± 1.9 kg/m².

In Chen et al work, In the aspirin responder group the mean BMI was 25.4 with SD ± 3.1, while in aspirin resistant group the mean BMI was 26.9 with SD ± 3.9. Yet this was statistically **non significant** difference.

Theoretically, body mass index and insulin resistance (metabolic syndrome) may affect the level of platelet activity and blunt aspirin's effect. ***(Deepak L. Bhatt, 2004)***

IV- Hypertension:

In this study, **There was no statistical significant difference in both groups as regards history of hypertension**. Aspirin responders group included 65 (74%) hypertensive patient and 23 (26%) patients with no history of hypertension, while in aspirin resistant group 8 (67%) were hypertensive with 4 (33%) patients with no history of hypertension.

In the work of Chen et al, 77% of aspirin responders were hypertensive while in aspirin resistant group 76% were hypertensive, this was statistically **insignificant** difference.

V- Cigarette smoking:

In our study, Aspirin responders group included 34 (39%) current smoker, 28 (32%) non smoker and 26 (29%) ex smoker, while in aspirin resistant group 10 (83.4%) smokers, 1 (8.3%) non smoker and 1 (8.3%) ex smoker. **Most patients in aspirin resistant group were current smokers**. Smoking was independent predictor for aspirin resistance.

This might be explained by the fact that cigarette smoking has been shown to accentuate platelet thrombosis in a way that is not inhibited by aspirin. ***(Deepak L. Bhatt, 2004)***. However,

Gum et al work showed that patients with aspirin resistance are less likely to be smokers, as 17% of aspirin responder patients were tobacco smokers while 0% of aspirin resistant patient were smokers, this difference was statistically **non** significant.

VI- DM:

In this study, **aspirin resistance was more common among diabetic patients especially IDDM patients**.

Aspirin responders group included 25 (28%) NIDDM patients, 19 (22%) IDDM patients and 44 (50%) non diabetic patients, while in aspirin resistant group 2 (17%) patients were NIDDM, 7 (58%) patients were IDDM, 3 (25%) patients were non diabetic.

The explanation of the effect of DM on aspirin responsiveness may be that hyperglycemia may decrease the effectiveness of antiplatelet therapy by increasing reactive oxidant species. Aspirin is thought to inhibit platelet aggregation primarily by inactivating the cyclooxygenase (COX), thus decreasing the synthesis of the pro-aggregatory arachidonic acid metabolite thromboxane A2. However, recent studies also identified a non-enzymatic, oxidation-dependent pathway for the synthesis of the arachidonic acid derivative isoprostanes, which exhibit potent vasoconstrictor and pro-aggregatory effects similar to that of TxA2. Because the pathophysiological conditions that promote arteriosclerotic vascular diseases (e.g. hypercholesterolemia, diabetes mellitus, hyperhomocysteinemia) are thought to be associated with an increased formation of reactive oxygen species and increased plasma isoprostane levels, it can be hypothesized that increased COX-independent isoprostane formation in platelets contribute to Aspirin resistance. ***(Csiszar A et al., 2002)***

In both the work of Gum et al and Chen et al, there were **no** statistical significant difference between aspirin resistant and responders as regards presence or absence of diabetes.

In the work of Chen et al 40% of aspirin responders were diabetic while in aspirin resistant group 44.8% were diabetic, this trend was statistically **insignificant**.

In the work of Gum et al, 25% of aspirin responders were diabetic while in aspirin resistant group 18% were diabetic, again, again, this trend was statistically **insignificant**.

VII- Hypercholesterolemia:

In this study, **aspirin resistance was more common among dyslipidemic patients**, aspirin responders group included 51 (58%) dyslipidemic patients and 37 (42%) patients were non dyslipidemic, while in aspirin resistant group 10 (83%) patients were dyslipidemic with 2 (17%) patients were non dyslipidemic.

in the work of Chen et al, there was **no** statistical significant difference between aspirin resistant and responders as regards presence or absence of hyperlipidemia, 77.9% of aspirin responders had abnormal lipid profile while in aspirin resistant group 72.4% had abnormal lipid profile, this trend was statistically **insignificant**.

Theoretically hypercholesterolemia may blunt aspirin's effect on thrombin which might be due to:

1) Alterations in platelet lipid-protein matrix that render their membrane proteins less accessible for acetylation by aspirin.

2) Changes in composition and structure of plasma lipoproteins that diminish the chance of aspirin to interact with prothrombin. ***(Andrzej Szczeklik et al., 1996)***

VIII- Positive family history of premature atherosclerosis:

Genetics play a role in patient's response to aspirin. Polymorphisms of platelet membrane glycoproteins such as P1 (A1/A2) have been associated with an attenuated response to aspirin. Polymorphisms of von Willebrand Factor (vWF) or the

collagen receptor gene have also been postulated to cause aspirin resistance. ***(Sperr WR et al., 1998)***

However, in our study **There were no statistical significant difference in aspirin responsiveness as regards family history of premature atherosclerosis.**

Laboratory predictors:

Serum creatinine:

In our study, **Renal impairment was statistically significant more common among aspirin resistant group.** 88 patients included in this study has baseline S. creatinine less than 1.5 mg/dl, 12 patients had renal impairment with baseline Serum creatinine > 1.5 mg/dl. In the aspirin resistant group 6 (50%) patients had serum creatinine > 1.5 mg/dl, while in aspirin responders 6 (7%) patients had serum creatinine greater than 1.5 mg/dl. In the aspirin responder group the mean s. creatinine was 1.1 mg/dl, with SD ± 0.34 mg/dl, while in aspirin resistant group mean s. creatinine was 1.5 mg/dl, with SD ± 0.1 mg/dl.

In Chen et al work, the aspirin responder group had the mean serum creatinine 1.28 mg/dl, with SD ± 0.76 mg/dl, while in aspirin resistant group the mean serum creatinine was 1.4 mg/dl, with SD ± 0.52 mg/dl. This was statistically insignificant difference. In the aspirin responder patients, 11.5% had renal insufficiency, while in aspirin resistant patients 24.1% had renal insufficiency, again this was statistically insignificant difference.

Although salicylic acid is **removed** from the body by **renal** elimination of both free and metabolized drug, minor extra renal pathways account for less than 10% of the total dose, ***(Gatti G et al., 1989)*** this would lead to less aspirin clearance in patients with renal impairment, yet renal impairment patients have less antiplatelet effect than those with normal renal function, the explanation of the results is not clear yet.

Angiographic predictors:

Chen et al published the angiographic characteristics in relation to aspirin responsiveness as all patient underwent coronary angiography.

I- Lesion location:

In this study, aspirin responders group included 36 (40%) patients with the culprit lesion in the LAD, 31 (35%) patients had the culprit lesion in the LCx and 21 (24%) patients had the culprit lesion in the RCA, while in aspirin resistant group 6 (50%) patients had the culprit lesion in the LAD, 3 (25%) patients had the culprit lesion in the LCx and 3 (25%) patients had the culprit lesion in the RCA. **There was no statistical difference in both groups as regards lesion location.**

In Chen et al work**,** aspirin responders group (36.8%) patients with the culprit lesion in the LAD, (38.7%) patients had the culprit lesion in the LCx and (22.1%) patients had the culprit lesion in the RCA, with (2.5%) had the culprit lesion in the left main, while in aspirin resistant group (47.7%) of the patients had the culprit lesion in the LAD, (18.2%) of the patients had the culprit lesion in the LCx and (29.5%) patients had the culprit lesion in the RCA. with (4.5%) had the culprit lesion in the left main**. There was no statistical difference in both groups as regards lesion location.**

II- Reference vessel diameter (RVD):

In this study, aspirin responder group had mean RVD 3.03mm, with SD ± 0.292mm, while in aspirin resistant group the mean RVD was 2.9 mm, with SD ± 0.316 mm. **There was no statistical difference in both groups as regards RVD.**

In Chen et al work, aspirin responder group had mean RVD 2.66 mm, with SD ± 0.57 mm, while in aspirin resistant group the mean RVD was 2.51 mm, with SD ± 0.55 mm. **There was no statistical difference in both groups as regards RVD.**

III- Angiographic Severity of the lesion:

In this study, aspirin responder group had mean percentage of severity of the lesion of 89%, with SD ± 5%, while in aspirin resistant group mean percentage of severity of the lesion was 92% with SD ± 3.3%.

There were no statistical difference in both groups as regards mean percentage of severity of the lesion.

Chen et al did not publish the angiographic severity of the lesion.

IV- AHA lesion classification of the culprit lesion:

In this study, aspirin responders had culprit lesion with AHA type A in 58 (66%) patients, type B in 20 (23%) patients and type C in 10 (11%) patients while in aspirin resistant patients, culprit lesion was AHA type A in 7 (58%) patients, type B in 3 (25%) patients and type C in 2 (17%) patients. **There was no statistical significant difference in both groups as regards AHA classification of the culprit lesion.**

In Chen et al work, aspirin responders had culprit lesion with AHA type A/B1 in (20.9%) of the patients, type B2/C in (79.1%) of the patients while in aspirin resistant patients, culprit lesion was AHA type A/B1 in (25%) patients, type B2/C in (75%) of the patients. **There was no statistical significant difference in both groups as regards AHA classification of the culprit lesion.**

V-Thrombus containing lesion and aspirin responsiveness:

In this study, aspirin responders had culprit lesion angiographically not containing thrombus in 87 (99%) patients, thrombus containing in 1 (1%) patient, while in aspirin resistant patients culprit lesion was angiographically not containing thrombus in 11 (92%) patients, thrombus containing in 1(8%) patient. **There was no significant difference in both groups as regards thrombus content in the culprit vessel.**

In Chen et al work, aspirin responders had culprit lesion angiographically containing thrombus in (2.5%) of the patient, while in aspirin resistant patients culprit lesion was angiographically containing thrombus in (0%) of the patients. **There was no significant statistical difference in both groups as regards thrombus content in the culprit vessel.**

Outcomes according to aspirin responsiveness

1) Myonecrosis:

Many studies have demonstrated an association between aspirin resistance and long-term cardiac events. and, as aspirin resistance is linked to periprocedural MI. and aspirin resistance is linked to long-term adverse cardiovascular outcome, then some of the association between periprocedural MI and long-term outcome may be mediated by aspirin resistance.

Early complications of PCI are caused by arterial thrombosis at the site of vessel injury. More complete platelet inhibition using aspirin and a thienopyridine during PCI offers protection against ischemic complications. However, 5% to 60% of patients do not respond to aspirin therapy as determined by different laboratory tests, and these aspirin-resistant patients are at increased risk of thrombotic events.

Wai-Hong Chen et al performed the first study to demonstrate that, despite adequate pretreatment with clopidogrel, patients undergoing non urgent PCI are at increased risk of myonecrosis when they are determined to be aspirin-resistant using a point-of-care assay, compared with those who are aspirin-sensitive. Elevation of CK-MB has been shown to be associated with a higher incidence of death, myocardial infarction, and repeat revascularization after PCI. Prevention of post-PCI myonecrosis, therefore, is of clinical importance.

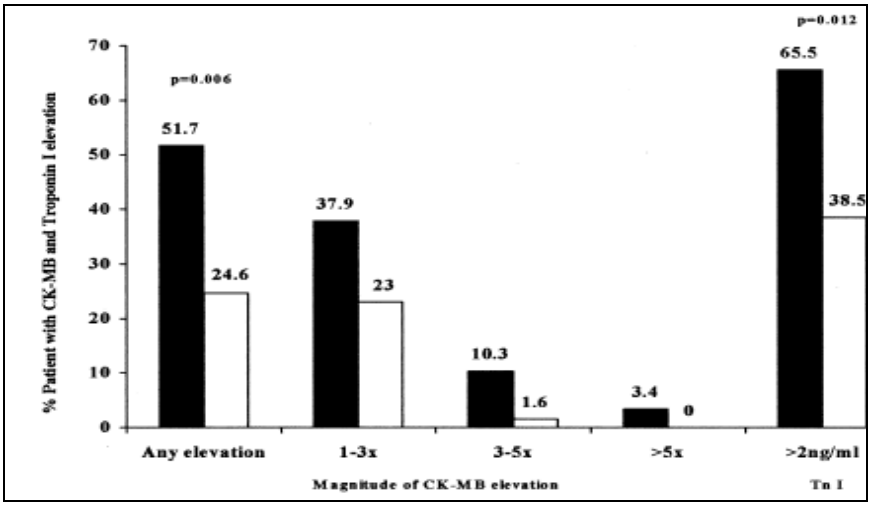


Figure 24. Patients with evidence of aspirin resistance at baseline are much more likely to have periprocedural myonecrosis during elective PCI. (Wai-Hong Chen et al., 2004)

Despite receiving the antiplatelet effect of clopidogrel with a 300-mg loading dose given >12 hours before non-urgent PCI, aspirin-resistant patients had a 2.9-fold increased risk of CK-MB elevation compared with aspirin-sensitive patients. Furthermore, in aspirin resistant group 51.7 % of the patients has post procedure CK MB elevation of them 37.9% had (1-3)x elevation, 23% had (3-5)x elevation and 3.4% had post procedural CK MB elevation > 5x. while in aspirin responder group 24.6 % of the patients has post procedure CK MB elevation, of them 23% had (1-3)x elevation, 1.6% had (3-5)x elevation and 0% had post procedural CK MB elevation > 5x. myonecrosis was more common and more severe in aspirin resistant group, yet it is only part of the story.

In our study we collected baseline **blood sample** for CK-MB few hours before the procedure. The CK-MB was considered elevated if ≥24mg/dl, patients with elevated baseline CK-MB were excluded. After the procedure by (8-12) hours another blood sample for CK-MB was taken. Post procedural CK-MB was further subdivided into 1 to 3 times the

upper limit of normal (up to 72 mg/dl), 3 to 5 times upper limit of normal (72-120 mg/dl), and >5 times upper limit of normal (>120 mg/dl) normal. **Periprocedural MI (Myonecrosis**) was defined if the post procedure CK MB is ≥3 times the upper limit of normal (ULN).

In aspirin responder group 25 (28%) patients had post procedure CK MB elevation > 3 times (myonecrosis), of theses patients only one patient (1.1%) had CK MB elevation > 5 times, 63 (72%) patients had CK MB elevation < 3 times (no myonecrosis), while in aspirin resistant group all (100%) patients had post procedure CK MB elevation > 3 times, 8 (66%) of them had CK MB elevation > 5 times. **Aspirin resistance was associated with higher incidence and more severe myonecrosis, also** there was a statistically highly significant positive correlation between myonecrosis and **platelet aggregation**, the higher the platelet aggregation the more post procedural CK MB rise even without reaching the threshold for the definition of aspirin resistance**.**

2) Angiographic evaluation of reperfusion:

Our study revealed better TIMI flow and higher MBG grade among aspirin responder patients.

I- Post procedure TIMI flow grade:

In this study, Aspirin responders group included 86 patients (98%) with post procedure TIMI III flow, only 2 (2%) patients had post procedure TIMI II flow. In aspirin resistant group TIMI III flow was achieved in 9 (75%) patients while 3 (25%) patients had post procedure TIMI II flow. **Aspirin responders had statistically significant better post PCI TIMI flow in the culprit lesion.**

In Chen et al work, All patients underwent successful PCI with TIMI flow grade 3 in the culprit vessel after the intervention.

II- Post procedure MBG:

In this study, Aspirin responders group included 84 (95%) patients with post procedure MBG 3, only 4 (5%) patients had post procedure MBG 2. In aspirin resistant group 8 (67%) patients had post procedure MBG 3, only 4 (33%) patients had post procedure MBG 2. **Aspirin responders had better post PCI MBG in the territory of the culprit vessel.** Chen et al did publish MBG post PCI in the culprit lesion.

3) Clinical follow up:

Clinical importance of aspirin resistance was evaluated in many studies.

In 1993 Grotemeyer KH et al found aspirin resistance incidence = 30% post stoke patients, 2 year follow-up of these patients showed an **89**% increase in the risk for a subsequent vascular event among aspirin resistant patients compared with aspirin responders.

In another study, ***Grundmann K et al*** studied the effect of aspirin resistance on the **secondary prevention of cerebrovascular stroke,** 53 patients on 100 mg aspirin daily, were included. Patients were categorized as asymptomatic if they were free of cerebrovascular incidents for at least 24 months. Symptomatic patients had suffered ischemic strokes or transient ischemic attacks. Platelet function was assessed using the PFA-100, closure times were significantly **shorter** in **symptomatic** patients than in **asymptomatic** patients.

Muller et al, studied Aspirin responsiveness in **peripheral vascular disease**. Among 100 patients underwent peripheral arterial angioplasty only 40% demonstrated appropriate platelet inhibition after 100 mg of aspirin. Importantly, aspirin non-responders had an **87**% increase in the risk of arterial re-occlusion during follow-up.

Eikelboom JW studied whether aspirin resistance, defined as failure of suppression of thromboxane generation, increases the risk of cardiovascular events in a high-risk population and it found that among aspirin-treated patients, those with higher concentrations of urinary 11-dehydro thromboxane B2 (a stable metabolite of thromboxane A2) had a **2-times** higher risk of myocardial infarction and a **3.5**-times higher risk of cardiovascular death.

Gum et al, reported the two-years follow-up of aspirin resistant patients After adjusting for 12 potential prognostic factors, multivariate analysis indicated that aspirin resistance was associated with a **4.1**-fold excess adjusted hazard of serious vascular events, independent of age, gender, and conventional vascular risk factors.

In our study, patients had mean follow up period of 12 months. Group I (aspirin responders) revealed 80 (90.9%) patients had event free 12 months follow up with 8 (10%) patients had events, 6 of these patients had recurrent chest pain (chronic stable angina, Canadian functional class III), two patients had transient ischemic attack (TIA). In group II (aspirin resistant) 8 (66.7%) patients had event free 12 months follow up with 4 (33.3%) patients had events, 2 of them had recurrent chest pain (chronic stable angina Canadian functional class III), one patient had transient ischemic attack, one patient was admitted to the hospital 50 days after the procedure with unstable angina.

During twelve months follow up aspirin resistant patients had statistically significant higher rates of adverse cardiovascular and cerebrovascular events than aspirin responders.

Conclusion

❖ Prevalence of aspirin resistance among patients included in this study was **12**%.

❖ Predictors of aspirin resistance included **age**, **smoking**, **renal impairment**, **diabetes mellitus**, **dyslipidemia** and **obesity**.

❖ Aspirin resistance had **no** statistically significant correlation with gender, hypertension, platelet count and positive family history of premature atherosclerosis.

❖ Aspirin resistance was more common among patients with multi-vessel disease.

❖ There was **no** statistically significant correlation between the RVD, anatomy of the culprit lesion and aspirin responsiveness.

❖ Despite adequate pretreatment with clopidogrel, aspirin resistance was associated with higher incidence and more severe form of myonecrosis.

❖ Aspirin responders had better TIMI flow and MBG.

❖ Aspirin resistant patients had significantly higher rates of adverse cardiovascular and cerebrovascular events.

❖ Even in aspirin responders, myonecrosis was positively correlated with platelet aggregation, the higher the platelet aggregation the more post procedural CK MB rise.

Recommendations

❖ Further studies are needed to test the prevalence of aspirin resistance among different population including patients with cerebrovascular disease, peripheral vascular disease and in general Egyptian population.

❖ Our results need to be confirmed on larger number of patients.

❖ Further studies are needed to test the effect of increase aspirin dose on the platelet aggregation tests in aspirin resistant patients for possible individualization of antiplatelet therapy especially for morbidly obese patients, diabetics, smokers, dyslipidemic patients and patients with chronic renal impairment.

❖ Further studies are needed to test the responsiveness of clopidogrel in aspirin resistant patients as dual drug-resistant patients may be at increased risk for thrombotic complications after PCI.

❖ Dose adjustment of aspirin might be recommended in morbidly obese patients, diabetics, smokers, dyslipidemic patients and patients with chronic renal impairment.

❖ The problem of aspirin resistance is not a rare phenomenon, it might be worthy to perform platelet function tests before proceeding for high risk PCI such as those with left main stenting or who had previous stent thrombosis as it might affect both short and long term clinical and angiographic outcomes.

Limitations of the this work

❖ Aspirin use was based on answers to questionnaires. Salicylate levels or pill counts were not performed.

❖ The population of the study were patients with stable ischemic heart disease, so the incidence of aspirin resistance among general population may differ from its incidence in this study, also patients with unstable angina and those with congestive heart failure may have different results.

❖ Aggregation studies were performed only at baseline, and it is possible that response to aspirin is variable. A single baseline measurement may not reflect the extent of platelet inhibition over long periods of time.

❖ Although our study demonstrated an association between aspirin resistance and long-term clinical events, the overall number of events was small.

Summary

Platelets play a life-saving role in thrombosis, Thus, anti-platelet therapy has become a mainstay in treatment and prophylaxis of conditions like myocardial infarction, stroke and other cardiovascular diseases. ***(Mayr FB et al., 2006)***.

Over the years antiplatelet treatment has evolved and currently several types of antiplatelet drugs are available, each with their specific pharmacological target and with their specific clinical indications. ***(N Clappers et al., 2007).***

Overall, approximately 20 different agents have been shown to inhibit platelet aggregation through different mechanisms of action. ***(Carlo patrono et al., 2004)***

Acetyl salicylic acid was first synthesized and introduced into clinical practice at the end of the 19th century. ***(Vane JR et al., 1990)***

Currently, aspirin is recommended by American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) guidelines as a first-line antiplatelet agent for different indications. ***(Xi Cheng et al., 2006)***.

Today aspirin has been the most widely used drug in the world, initially for its antipyretic and antirheumatic properties and for its Antithrombotic effects. ***(Shahar E et al., 1996)***

Low-dose daily aspirin is clearly a useful therapy for primary and secondary prevention of cardiovascular events. Aspirin is easy to give, inexpensive, and has relatively few side effects at low doses. Therefore, aspirin is unlikely to ever be replaced as a first-line antiplatelet agent. ***(Scott A. McKee et al., 2002)***

Though we typically focus on the 22% relative risk reduction in virtually every group with aspirin therapy, we can also look at it from the angle of the 80% of patients at risk who had an event despite aspirin therapy. ***(Steven R. Steinhubl. 2003)***

There are several reasons why aspirin may not be totally effective in preventing recurrent serious vascular events. One possible explanation that has recently attracted great interest is that some patients are resistant to the antiplatelet effects of aspirin. The term "**aspirin resistance**" has evolved to describe the failure of aspirin to produce an expected response on one or more laboratory measures of platelet activation and aggregation. ***(John W. Eikelboom., 2003)***

Aspirin resistance was associated with worse outcomes in many clinical trial. **(Gum et al, *Grundmann K et al* and *Eikelboom JW et al).***

Wai-Hong Chen et al found that patients undergoing elective PCI who were classified as aspirin resistant at baseline were likely to develop periprocedural myonecrosis.

Other studies have demonstrated an association between aspirin resistance and long-term cardiac events. Thus, if aspirin resistance is linked to periprocedural MI and aspirin resistance is linked to long-term adverse cardiovascular outcome, then some of the association between periprocedural MI and long-term outcome may be mediated by aspirin resistance. ***(Deepak L. Bhatt et al., 2005)***

In this study efforts were exerted to detect the prevalence of aspirin resistance among patients with IHD undergoing elective PCI, predictors of aspirin resistance and its impact on myonecrosis, angiographic outcomes and clinical follow up.

In 100 patients included in the study. The prevalence of aspirin resistance among population of the study was 12%.

Clinical predictors of aspirin resistance included: older age, obesity, DM and dyslipidemia.

There was a statistically significant positive correlation between serum creatinine and platelet aggregation, the higher serum creatinine the less platelet inhibition by aspirin.

Angiographic predictors of aspirin resistance was the presence of multi-vessel disease.

Aspirin resistance was associated with statistically significant higher incidence and more severe myonecrosis. There was a statistically highly significant positive correlation between myonecrosis and platelet aggregation, the higher the platelet aggregation the more post procedural CK MB rise even without reaching the threshold for the definition of aspirin resistance.

Aspirin responders had better post PCI TIMI flow in the culprit lesion and better post PCI MBG in the territory of the culprit vessel.

During mean period follow up of 12 months, aspirin resistant patients had significantly higher rates of cardiovascular and cerebrovascular events than aspirin responders.

So should we move toward a situation where we routinely measure response to antiplatelet drugs, like we do with lipid-lowering and antihypertensive medications? There is no other area in cardiology where we just give one dose of a drug and hope for the best, as in 21st century no place for "one dose fits all". ***(Victor L. Serebruany et al., 2005)***

Further studies are needed to test the prevalence of aspirin resistance among different population including patients with cerebrovascular disease, peripheral vascular disease and in general Egyptian population.

Further studies are needed for assessment of the cost effectiveness of individualization of antiplatelet therapy.

Dose adjustment of aspirin might be recommended in morbidly obese patients, diabetics, smokers, dyslipidemic patients and patients with chronic renal impairment.

It might be worthy to perform platelet function tests before proceeding for high risk PCI such as those with left main stenting or who had previous stent thrombosis as it might affect both short and long term clinical and angiographic outcome.

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الملخص العربى

تعتبر مضادات الصفائح الدموية علاج أساسي لمرضى القلب. بالأخص الأسبرين الذي يعتبر أكثر الأدوية شيوعا. حيث أثبت الأسبرين فاعلية كبرى فى علاج مرضى القصور بالدورة الدموية التاجية سواء في حالات احتشاء عضلة القلب الحاد أو حالات الذبحة الصدرية المستقرة.

الآن بعد مرور أكثر من مائة عام على تصنيع و تسويق عقار الأسبرين يعتبر الأسبرين أوسع العقارات انتشارا حيث يستهلك منه في الولايات المتحدة الأمريكية حوالي 35000 كجم يوميا.

وأكدت الدراسات أثر الأسبرين على خفض نسبة الوفيات في علاج حالات الاحتشاء الحاد بعضلة القلب بمقدار الربع من خلال المتابعة لمدة 35 يوماً.

بشكل عام تتراوح جرعة الأسبرين من 80 إلى 325 مجم مره واحدة يوميا لتحقيق السيولة الكافية لمرضى قصور الشرايين التاجية.

يقوم الأسبرين بدوره العلاجي عن طريق منعه تكوين مادة الثرومبوكسان في الصفائح الدموية.

على الرغم من كون الأسبرين من أكثر الأدوية التي تمت دراستها في أمراض القلب خلال القرن الماضي، فان مقاومة تأثير عقار الأسبرين ظاهرة حديثة الاكتشاف.
مقاومة عقار الأسبرين تعنى أن المريض يتناول عقار الأسبرين بدون تحقيق سيوله كافيه للدم.

يتزايد الاهتمام بمقاومة عقار الأسبرين هذه الأيام في الأوساط الطبية وخاصة المهتمين بأمراض القلب والشريان التاجي ، والجلطات المخية ولكن إلي الآن لم يتم عمل دراسة كبرى لتحديد الكيفية المثلى لقياس الاستجابة لعقار الأسبرين.

في إحدى الدراسات الكبرى تم قياس تأثير عقار الأسبرين عن طريق قياس مادة 11 دى هيدروثرمبوكسان ب 2 في البول ووجد أن المرضى اللذين يحقق لهم الأسبرين سيوله أقل تحدث بهم المضاعفات مثل احتشاء عضلة القلب وجلطات المخ بشكل أعلى.
قد يحدث ارتفاع طفيف في إنزيمات القلب CK-MB مصاحبا للقسطرة التداخلية للشريان التاجي ما يسمى (الاحتشاء الدقيق) بنسبة تتراوح من 10 إلى 40 % من

الحالات, وقد أثبتت الدراسات انه في حالات ارتفاع إنزيمات القلب تكون مصاحبه بعوامل خطورة أكبر تصل إلى الوفاة في خلال المتابعة لمدة 3 سنوات وهذا قد يفسر بـ تأثير الاحتشاء الدقيق على كفاءة البطين الأيسر أو الاستقرار الكهروفسيولوجى للقلب.

أحد الدراسات الجديدة درست العلاقة ما بين حدوث مقاومة تأثير عقار الأسبرين مع احتمالية حدوث الاحتشاء الدقيق ما بعد القسطرة التداخلية وبدراسة نتائج هذه الدراسة وجد انه في المرضى اللذين يعانون من مقاومة تأثير عقار الأسبرين تكون نسبة حدوث الاحتشاء الدقيق لعضلة القلب نسبة اكبر مما يعرضهما إلى معامل خطورة أعلى.

الهدف من الدراسة

1) تحديد نسبة حدوث مقاومة عقار الأسبرين في مرضى قصور الشريان التاجي المقرر لهم قسطرة تداخلية غير عاجلة.
2) دراسة تأثير مقاومة عقار الأسبرين على نسبة حدوث الإحتشاء الدقيق بعد القسطرة التداخلية غيرا لعاجلة.
3) دراسة النتائج التصويرية للقسطرة التداخلية غيرا لعاجلة في مرضى المصابين بمقاومة عقار الأسبرين.
4) دراسة النتائج و المتابعة الإكلينيكية للمرضى خلال 12 شهر.

شملت هذه الدراسة على 100 مريض مصابين بقصور الشريان التاجي تم لهم إجراء قسطرة قلبية تداخلية غير عاجلة في مستشفيات جامعة عين شمس.
و قد خضع جميع المرضى للآتي:
أخذ التاريخ المرضى، فحص إكلينيكي دقيق، موجات فوق صوتية على القلب، سحب عينة الدم قبل القسطرة التداخلية لعمل تحليل اختبار مقاومة عقار الأسبرين و تحليل إنزيمات القلب ثم سحب عينة الدم 8 ساعات بعد القسطرة التداخلية لعمل تحليل إنزيمات القلب.

تمت دراسة النتائج التصويرية للقسطرة التداخلية و معدل سريان الدم في الشريان التاجي المصاب.

تمت دراسة النتائج و المتابعة الإكلينيكية للمرضى في خلال 12 شهر من حيث حدوث احتشاء عضلة القلب، جلطة بالمخ، ذبحة صدرية أو الوفاة.

وجدنا في هذه الدراسة أن نسبة انتشار مقاومة تأثير عقار الأسبرين بين المرضى المشاركين تصل إلى 12%.

مقاومة تأثير عقار الأسبرين كانت أكثر شيوعا بين المرضى الأكبر سنا، المدخنين، مرضى السكر، مرضى ارتفاع الدهون بالدم و مرضى السمنة المفرطة.

مقاومة تأثير عقار الأسبرين كانت أكثر شيوعا بين المرضى الذين يعانون من الإصابة في أكثر من شريان من الشرايين التاجية.

وجدنا ارتباط احصائى عكسي بين وظائف الكلى (بقياس نسبة الكرياتينين) و تأثير عقار الأسبرين، كلما ارتفعت نسبة الكرياتينين في الدم كلما قلت استجابة الصفائح الدموية لعقار الأسبرين.

مجموعة المرضى الذين تم اكتشاف أنهم مقاومين لعقار الأسبرين حدث لهم الاحتشاء الدقيق بنسبة أعلى من باقي المرضى.

معدل تدفق الدم ما بعد توسيع الشريان التاجي و مؤشرات إعادة الارتواء كانت أقل في مجموعة مرضى مقاومة تأثير عقار الأسبرين.

خلال فترة المتابعة الاكلينيكية، عانت مجموعة المرضى الذين تم اكتشاف أنهم مقاومين لعقار الأسبرين من مضاعفات بالدورة الدموية التاجية و الدماغية بشكلى أعلى من باقي المرضى.

نحن نوصي بالمزيد من الدراسات على أعداد أكبر من المرضى و مجموعات مختلفة من المرضى (قصور الدورة الدموية الدماغية ، قصور الدورة الدموية الطرفية و عامة الناس).

كذلك مطلوب المزيد من الدراسات لتعديل جرعات الأسبرين و غيره من مضادات الصفائح الدموية على حسب نتائج تحليل وظائف الصفائح الدموية بالذات في المرضى الذين يخضعون لتوسيع الشريان التاجي بالقسطرة عالية الخطورة مثل تدعيم الشريان الأيسر الرئيسي.

نسبة حدوث مقاومة تأثير عقار الأسبرين و تأثيرها على نتائج القسطرة التداخلية فى مرضى قصور الدورة الدموية التاجية من حيث حدوث الاحتشاء الدقيق، النتائج التصويرية و المتابعة الاكلينيكية على المدى الطويل

رسالة مقدمه توطئه لنيل درجة
الدكتوراة فى امراض القلب و الاوعيه الدمويه
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