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Predicting of Medication Adherence Using Morisky Medication Adherence Scale and Analytical Evaluation of Antiplatelet Medications Available in Libya

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ABSTRACT

Patients adherence to their healthcare protocols is important to reach the best health outcomes. However, little attention has been given to the assessment of psychometric properties of adherence measures in Libyan population.

The study aimed to conduct a comprehensive work for evaluation the relationship between patients noncompliance and medication satisfaction of patients on Clopidogrel, to investigating the argument of][Libyan physicians. Also, the quality of 4 brands of Clopidogrel is described and compared to the quality of the innovator drug product (PLAVIX ®) in order to support the study.

Adherence of patients on various brands of Clopidogrel available in Libyan market were examined by 8-item Morisky Medication Adherence Scale. And four generic alternatives of Clopidogrel were compared to the innovator drug product for weight variation, thickness, hardness, disintegration and dissolution.

Patients on different brands of Clopidogrel were randomly selected (n=200), Their mean ages of the study sample was 63 ±10 years. Participants from Tripoli-City hospitals completed an in-person interview assisted questionnaire. The questionnaire was the 8-item Morisky Medication Adherence Scale (MMAS-8). The reliability and validity of the measures were also evaluated.

The study found that more than half of patients on Plavix® and Apo-Clopidogrel® reported a high level of adherence 59%, 56% respectively. While about 72% of the patients on other brands of Clopidogrel reported low to medium level of adherence. The present study showed that the 8-item MMAS had good reliability (Cronbach's alpha= 0.755). Additionally, the exclusion of the "feel hassled by treatment plan," item improved the overall reliability slightly (46% indicating "feel hassled by treatment plan"). There is a statistically significant relationship (p=0.05) between patients' adherence behaviour and their gender. The study revealed that males have higher adherence toward taking their medication compared to females (53%, 36% respectively).

The results clearly indicate that four brands of Clopidogrel tablets comply with the pharmacopeia standards set for these products for weight variation, thickness, hardness and dissolution except Antiplex® tablets which failed in thickness, hardness and dissolution tests.

The study concluded that the patients on different brands of Clopidogrel "who had been described by physicians in having low medication efficacy" reported low medication adherence. The quality analysis tests reinforce the previous findings. This proves why the innovator Plavix® is more effective than other generic alternatives. It is also mandatory for manufacturers and all other key players in the drug distribution business to assure that final products reach consumers with high quality and efficacy. This is only possible in an environment of high ethical and moral standards.

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LIST OF ABBREVIATIONS

ADP	Adenosine diphosphate
A	Angstrom
BMQ	Brief Medication Questionnaire
ºC	Degree centigrade
$	Dollars
Fig.	Figure
g	Gram
hr	Hour
IVIVC	In-Vivo In-Vitro Correlation
Kg	Kilogram
MAQ	Medication Adherence Questionnaire
MARS	Medication Adherence Rating Scale
mg	Milligram
mm	Millimetre
min	Minutes
MI	Myocardial infarction
MMAS	Morisky Medication Adherence Scale
nm	Nanometer
N	Newton (as unit of hardness)
N	Normality (as unit of concentration)

No.	Number
%	Percentage
PCI	Percutaneous coronary intervention
Ib	Pound-mass
pH	Power of hydrogen
%Q	Percentage of amount released of active ingredient in certain media at specific time
Ref.	Reference
rpm	Round per minute
SEAMS	The Self-efficacy for Appropriate Medication Use Scale
SPSS	Statistical Program for Social Sciences
Sec	Seconds
USP	United States Pharmacopeia
UV	Ultraviolet
WHO	World health organization

Chapter - 1

Introduction

1. Introduction

The study hypothesis depend upon believe that Libyan physicians do not prescribe any brand of Clopidogrel, with the exception of the innovator Plavix®. Substituting medication for their generic alternatives can affect patient's response and adherence to that medication, or it may result in adverse events [1]. For example, a Low response to clopidogrel and high post-treatment platelet reactivity at the time of Percutaneous coronary intervention (PCI) were identified as factors associated with poor clinical outcomes [2], but reliable tests are needed to identify low responders.

Patient adherence to their healthcare protocols is important to encourage the best health outcomes [3]. However, little attention has been given to assessing the psychometric properties of adherence measures in the Libyan population.

1.1. Medication adherence

The participants at the WHO Adherence meeting in June 2001 [4] concluded that defining adherence as "the extent to which the patient follows medical instructions" was a helpful starting point. However, the term "medical" was felt to be insufficient in describing the range of interventions used to treat chronic diseases. Furthermore, the term "instructions" implies that the patient is a passive, acquiescent recipient of expert advice as opposed to an active collaborator in the treatment process. Therefore Medication non-adherence or noncompliance is failure to take medications on time, in the prescribed dose, and by the correct patient, is costly in terms of economic loss and poor health outcomes".

The adherence project has adopted the following definition of chronic diseases: "Diseases which have one or more of the following characteristics: they are permanent, leave residual disability, are caused by nonreversible pathological alteration, require special training of the patient for rehabilitation, or may be expected to require a long period of supervision, observation or care" [5].

1.1.1. The impact of poor adherence

It is both medical (loss of immediate and/or long-term benefits) and economic (direct and indirect costs). Adhering and remaining engaged with daily drug treatment appears

to be a challenge for chronic patients [6]. The rate of non-adherence, to taking medications as prescribed, is estimated to be 30% to 50% in the United States [7].

Non-adherence to medications is common for patients with cardiovascular diseases [8]. Premature discontinuation of and reduced adherence to antiplatelet therapy have been identified as major risk factors for stent thrombosis and poor prognosis after acute coronary syndrome. Also non-adherence with Clopidogrel after coronary stenting is associated with increased mortality and myocardial infarction [9].

Absolute and relative risk assessments demonstrate that a considerable proportion of all cardiovascular disease events (9% in Europe) could be attributed to poor adherence to vascular medications alone. Measures to enhance adherence to help maximize the potentials of effective cardiac therapies in the clinical setting are urgently required [10].

Treatment failure may be associated with significant adverse outcomes including death, myocardial infarction (MI), cerebrovascular accident, closure of saphenous vein grafts, and occlusion of peripheral arterial grafts [11]. However, there is a growing evidence that despite this antiplatelet therapy some patients experience more atherothrombotic events than expected. This therapeutic failure has been called 'Clopidogrel resistance' [12, 13]. But treatment failure may result from patient noncompliance and/or inadequate response to the antiplatelet action of Clopidogrel [14].

Non-adherence is not solely a patient's problem, but impacts both the healthcare providers and the healthcare system. The first step toward improving adherence is broader recognition of the problem of non-adherence, and once identified, simple strategies should be implemented in daily practice to improve adherence [15].

1.1.2. Factors affecting therapeutic compliance

The ultimate aim of any prescribed medical therapy is to achieve certain desired outcomes in the patients concerned. These desired outcomes are part and parcel of the objectives in the management of the diseases or conditions. However, despite all the best intention and efforts on the part of the healthcare professionals, those outcomes might not be achievable if the patients are non-compliant. This shortfall may also have serious and detrimental effects from the perspective of disease management. Hence, therapeutic compliance has been a topic of clinical concern since the 1970s due to the widespread nature of non-compliance with therapy. Therapeutic compliance not only

includes patient compliance with medication but also with diet, exercise, or life style changes. In order to evaluate the possible impact of therapeutic non-compliance on clinical outcomes, numerous studies using various methods have been conducted in the United States (USA), United Kingdom (UK), Australia, Canada and other countries to evaluate the rate of therapeutic compliance in different diseases and different patient populations [16]. The factors identified from the studies may be grouped into several categories, namely, patient-centered factors, therapy-related factors, healthcare system factors, social and economic factors, and disease factors (Table 1.1).

Table 1.1. Categories of factors identified from the literature review

Category	Factors
Patient-centered factors	Demographic Factors: Age, Ethnicity, Gender, Education, Marriage Status
	Psychosocial factors: Beliefs, Motivation,Attitude
	Patient-prescriber relationship
	Health literacy
	Patient knowledge
	Physical difficulties
	Tobacco Smoking or alcohol intake
	Forgetfulness
	History of good compliance
Therapy-related factors	Route of administration
	Treatment complexity
	Duration of the treatment period
	Medication side effects
	Degree of behavioral change required
	Taste of the medication
	Requirements for drug storage
Healthcare system factors	Lack of accessibility
	Long waiting time
	Difficulty in getting prescriptions filled
	Unhappy clinic visits
Social and economic factors	Inability to take time off work
	Cost and Income
	Social support
Disease factors	Disease symptoms
	Severity of the disease

1.1.3. Methods of non-adherence measurement

Systematic diagnosis of non-adherence is crucial in investigating its impact on clinical outcomes and this can be carried out by direct and indirect methods. Direct methods include observation of the patient taking the medication, measurement of levels of the medication or metabolite in plasma or urine, and measurement in plasma of biologic markers added to the drug formulation. Indirect assessments include: patient self-report, patient questionnaires, assessment of clinical response, pill counts, use of pharmacy databases to determine refill rates and intervals, electronic medication monitors, and patient or caregiver diaries. Each of these strategies has strengths and limitations [17]. Of the currently available tools, the questionnaires are considered among the most useful and appropriate for the specific purpose of assessing the patient's adherence to prescribed medication [18].

1.1. 4. Scales used in Measuring Medication Adherence

Six adherence scales were identified. The Medication Adherence Questionnaire (MAQ) is the shortest scale and easiest to score. MAQ identifies barriers to nonadherence but not self-efficacy. The Self-efficacy for Appropriate Medication Use Scale (SEAMS) is a 13-question scale, and the Brief Medication Questionnaire (BMQ) has three main question headings and multiple subquestions. Both assess barriers and self-efficacy; however, scoring is difficult. The Hill-Bone Compliance Scale and Medication Adherence Rating Scale (MARS) address barriers and self-efficacy but are limited in their generalizability. The Hill-Bone Compliance Scale focuses on hypertensive patients, while MARS is specific to psychiatric populations **[19]**. The Morisky Medication Assessment Scale (MMAS) was developed by Donald Morisky and colleagues (1986) and has been validated in a number of studies, and this scale looks at motivation and knowledge that assists in determining the degree of patients adherence to their medication [17, 20, 21].

In 2008, the MMAS-8 was updated with greater sensitivity and higher reliability and specificity from the original four-item Morisky scale published in 1986 [22].

1.1.5. Advantages of Morisky Medication Adherence Scale (MMAS)

The MMAS-8 is considered the most commonly used self-reporting method in determining adherence, contains eight questions with closed dichotomous (yes / no)

answers [23, 24]. The patients were considered adherent when the result shows a score equal to 8 at the MMAS-8 [25, 26]. Also, it has become popular and commonly used in various clinical settings and different populations, as well as been translated and validated in foreign countries. Morisky scale hold advantages over other patient self-report instruments such as widespread use in different diseases, populations and countries, higher degree of concordance with pharmacy fill data or electronic monitoring devices, less items resulting in less response burden, and it has good screening and monitoring tools in clinical practice to identify and monitor the high-risk non-adherent patients [22].

93% sensitivity and 53% specificity were reported while validating in "very low income minority patients treated for hypertension seeking routine care in a clinic setting" [27]. MMAS was also validated with outstanding validity and reliability in patients with other chronic diseases [22]. As a result, it is probably the most accepted self-report measure for adherence to medication, simple, practical, and suitable for cardiovascular diseases. Along with blood pressure control data, MMAS should be able to identify medication nonadherence and help control blood pressure [27]. Therefore, it is recommended to serve as a screening tool for validated conditions in the clinic setting.

1.2. Pharmacology and clinical use of Clopidogril

Clopidogrel is an antiplatelet agent which selectively inhibits the binding of adenosine diphosphate (ADP) to its platelet receptor and blocks the subsequent ADP-mediated activation of the glycoprotein GPIIb/IIIa complex, thereby inhibiting platelet aggregation as shown in Fig 1.1 [28].

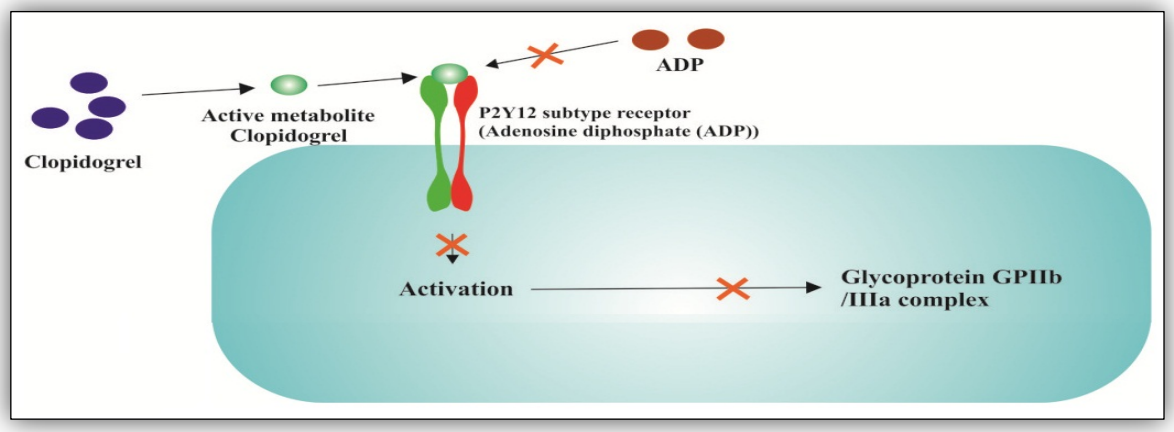
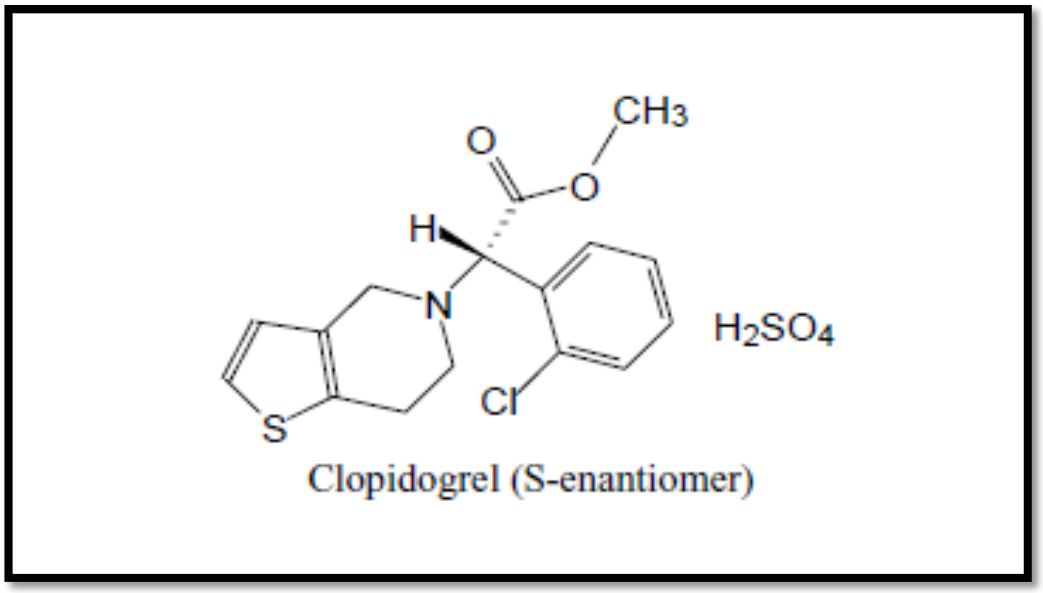


Fig 1.1. Clopidogrel mechanism of action

For the prophylaxis of thromboembolic events, the usual dose of clopidogrel is 75 mg once daily. In the management of acute coronary syndromes, including unstable angina and non-Q wave myocardial infarction, clopidogrel is given as a single 300-mg loading dose, followed by 75 mg once daily [29].

The innovator drug product containing clopidogrel (named hereafter clopidogrel) was discovered by Sanofi. It is marketed by Sanofi– Synthelabo worldwide under the brand names PLAVIX®.

The clinical benefits of clopidogrel have been demonstrated in trials involving more than 30,000 patients and it is used worldwide for the long term prevention of atherothrombotic events (myocardial infarction, stroke, peripheral arterial disease, acute coronary syndrome, cardio-vascular death) [30, 31]. As seen in Fig 1.2, the molecule is a thienopyridine derivative containing an assymetric carbon leading to the existence of two enantiomers (R and S). Many studies including Sanofi–Synthelabo study, showed that the active compound clopidogrel is the S-enantiomer. This implies that the content of the R-enantiomer must be carefully controlled in clopidogrel bulk substance and drug products, as required by health authorities [32, 33, 34].



Clopidogrel (S-enantiomer)

Fig 1.2. Chemical structure of Clopidogrel

1.3. Quality standard of compressed tablets

In addition to the apparent features of tablets, tablets must meet other physical specifications and quality standards. These include criteria for weight, weight variation, content uniformity, thickness, hardness, disintegration, and dissolution. These factors must be controlled during production and verified after the production to ensure that established product quality standards are met [35].

1.3.1. Tablet weight and USP weight variation

The quantity of fill in the die of a tablet press determines the weight of the tablet. The volume of fill is adjusted with the first few tablets to yield the desired weight and content. For example, if a tablet is to contain 20 mg of a drug substance and if 100,000 tablets are to be produced, 2,000g of drug is included in the formula. After the addition of the pharmaceutical additives, such as the diluents, disintegrant, lubricant, and binder, the formulation may weight 20kg, which means that each tablet must weight 200mg for 20mg of drug to be present. Thus, the depth of fill in the tablet die must be adjusted to hold a volume of granulation weighting 200mg. During production, sample tablets are periodically removed for visual inspection and automated physical measurement [36].

The USP contains a test for determination of dosage form uniformity by weight variation [37]. In the test, 10 tablets are weighed individually and the average weight is calculated assuming homogeneous drug distribution [35].

1.3.2. Tablet thickness

The thickness of a tablet is determined by the diameter of the die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the force or pressure applied during compression.

To produce tablets of uniform thickness during and between batch productions for the same formulation, care must be exercised to employ the same factors of fill, die, and pressure. The degree of pressure affects not only thickness but also hardness of the tablet. Hardness is perhaps the more important criterion since it can affect disintegration and dissolution. Thus, for tablets of uniform thickness and hardness, it is doubly important to control pressure. Tablet thickness may be measured by hand gauge during production or by automated equipment [35].

1.3.3. Tablet hardness

It is fairly common for a tablet press to exert as little as 3,000 and as much as 40,000lb of force in production of tablets. Generally, the greater the pressure applied, the harder the tablets, although the characteristics of the granulation also have a bearing on hardness. Certain tablets, such as lozenges and buccal tablets that are intended to dissolve slowly are intentionally made hard; other tablets, such as those for immediate drug release, are made soft. In general, tablets should be sufficiently hard to resist breaking during normal handling and yet soft enough to disintegrate properly after swallowing.

Several devices operating to test tablet hardness including special dedicated hardness testers or multifunctional systems are used to measure the degree of force (in kilograms, pounds, or in arbitrary units) required to break a tablet. A force of about 4 kg is considered the minimum requirement for a satisfactory tablet. Multifunctional automated equipment can determine weight, hardness, thickness, and diameter of the tablet [35,38].

1.3.4. Tablet disintegration

For the medicinal agent in a tablet to become fully available for absorption, the tablet must first disintegrate and discharge the drug to the body fluids for dissolution. Tablet disintegration also is important for tablets containing medicinal agents (such as antacids and antidiarrheals) that are not intended to be absorbed but rather to act locally within the gastrointestinal tract. In these instances, tablet disintegration provides drug particles with an increased surface area for activity within the gastrointestinal tract.

All USP tablets must pass a test for disintegration, which is conducted in vitro using a testing apparatus [38].

The apparatus consists of a basket and rack assembly containing six open-ended transparent tubes of USP-specified dimensions, held vertically upon a 10-mesh stainless steel screen.

During testing, a tablet is placed in each of the six tubes of the basket, and through the use of a mechanical device, the basket is raised and lowered in the immersion fluid at 29 to 32 cycles per minute, the wire screen always below the level of the fluid. For uncoated tablets, buccal tablets, and sublingual tablets, water at about 37C^{o} serves as the

immersion fluid unless another fluid is specified in the individual monograph. For these tests, complete disintegration is defined as "that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core" [37]. Tablets must disintegrate within the times set forth in the individual monograph, usually 30 minutes for the majority of the tablets but un coated tablets have disintegration time standards as low as 5min. Enteric coated tablets are to show no evidence of disentigrstion after one hour in stimulated gastric fluid, If one or more tablets fail to disintegrate, additional tests prescribed by the UPS must be performed [38].

1.3.5. Tablet dissolution

Another important part of the quality control is the release of the active ingredient from its pharmaceutical formulation, in this case a tablet. In most cases an in vitro dissolution test using paddles is performed to check whether a minimum percentage is dissolved at a predetermined time point. However, dissolution profiles with an equal percentage dissolved at a certain time point can have a different shape before reaching that time point, which, from a pharmacokinetic point of view, can lead to a difference in plasma concentrations [32].

The goal of in vitro dissolution testing is to provide insofar as is possible a reasonable prediction of or correlation with the product's in vivo bioavailability. The system relates combinations of a drug's solubility (high or low) and its intestinal permeability (high or low) as a possible basis for predicting the likelihood of achieving a successful in vivo-in vitro correlation (IVIVC) [39].

1.4. Aim of the study

The study aimed to conduct a comprehensive work for evaluation the relationship between patients noncompliance and medication satisfaction of patients on Clopidogrel, to ***investigating the argument*** of Libyan physicians.

In order to support the study on whether the arguments of physicians is correct or wrong, the quality of 4 brands of Clopidogrel is described and compared to the quality of the innovator drug product (PLAVIX ®) for the mass uniformity, thickness, hardness, disintegration and dissolution profiles.

Other Subsidiary objectives are:

- Compare the adherence in male with the adherence in female.
- Looking for the different causes of non- adherence.
- Study the relationship between the gender and their occupation.
- Also the reliability and the item to total correlation of questionnaire were examined.

Chapter - 2

Materials and Methods

2. Materials and Methods

2.1. Adherence

The study was carried out on patients have been treated with Clopidogrel at different hospitals within Tripoli- Libya, such as TRIPOLI MEDICAL CENTER, AL-MUSTAQBEL AL-MOSHREQ CENTER and NATIONAL HEART CENTER. Their ages were between 34-90 years and informed consent was obtained from all patients before being enrolled into study. These patients were selected by simple randomization method and given a questionnaire during a ten months period from 29/May/2104 to 2/February/2015. And only patients treated for more than two weeks were included in the study, and the questioner was excluded if any data missed during collection of information. All information related to the questionnaire and which brands of Clopidogrel the patients were taken, have collected face to face from patients themselves or their caregivers. The patients ' files were used to know if the patient was on Clopidogrel before collection of questionnaire information.

Adherence was determined by the MMAS-8 version, which translated for this study and because such questionnaire is used first time in Libya, the reliability and the item to total correlation of it were examined. The questionnaire contains eight questions with closed dichotomous (yes / no) answers. Thus, each item measured a specific adherence behavior, with seven questions that must be answered negatively and only one positively, with the last question being answered according to a scale of five options: never, almost never, sometimes, often, and always. The degree of adherence was determined according to the score resulting from the sum of all the correct answers. The total score of the MMAS-8 ranged from 0 to 8. Medication adherence of these instruments was trichotomised into three levels of adherence: high adherence (total score=8), medium adherence (6 to < 8) and low adherence (<6).

The study protocol was critically reviewed and approved by the Health Ethics Review Committee (Ministry of high education Tripoli- Libya).

Any brands of tablets containing Clopidogrel that patients use, were compared to the innovator drug product PLAVIX® (Sanofi Aventis, France) by using MMAS-8. And some of these brands shown in Table 2.1.

Table 2.1. Different brands of Clopidogrel available in Libyan market

Brand name	Pharmaceutical manufacturing company	Country of origin
Plavix ®	Sanofi Aventis	Turkey
Plavix ®	Sanofi Aventis	Italy
Apo- clopidogrel ®	Apotex	Canada
Clopidogrel	Akums	India
Instaclop ®	Ajanta house pharma	India
Clopidogrel	Clonmel	Ireland
Agregex ®	Actavis	Iceland
Clopi- Denk	Denk pharma	Germany
Clopidogrel Sandoz ®	Sandoz	Germany
Clopidogrel STADA®	STADA	Germany
Plavidosa ®	Specifar pharmaceuticals	Greece
Antiplex ®	Dar Al Dawa	Jordan
Plofexine ®	ASIA	Syria
Pedovex ®	Tabuk pharmaceutical	Saudi Arabia

2.2. Physical quality control tests

Beside the innovator Plavix®, a total of four alternatives bought from privet pharmacies hold sellers in Tripoli-Libya, were included in this study for brand comparison tests. The quality of four alternatives is described and compared to the quality of the innovator drug product (PLAVIX ®). Tablets from each brand were randomly visualized for the general appearance, size, shape, texture, colour uniformity and odour. Also, the weight variation, thickness, hardness, disintegration and dissolution profiles were examined in the Center for Food and Drug Control/ Tripoli.

The detailed specifications of these brands as indicated on the packaging (commercial name, manufacturer and country of origin of each product expressed as Clopidogrel base) are listed in Table 2.2.

Table 2.2. Overview of the samples used in this study

Sample	Product	Pharmaceutical company (country of origin)	Batch number
Ref. Clopidogrel	Plavix ®	Sanofi Aventis (France)	4A801
1	Plavix ®	Sanofi Aventis (Turkey)	AY014
2	Clopidogrel®	Clonmel Healthcare (Ireland)	N99998
3	Clopidogrel®	Actavis (Iceland)	F55802
4	Antiplex ®	Dar Aldawa (Jordan)	6677

The dose is 75 mg expressed as Clopidogrel base for all products

2.2.1. Weight variation, thickness and hardness tests:

Multifunctional automated equipment (combination tester- ERWEKA/ Germany) was used in determining the weight, hardness, thickness, and diameter of the tablet as shown in fig 2.1. Ten tablets from each brand were weighed individually the average weight of tablets were calculated. The % weight variation for the tablets was calculated using the equation:

$$\% \text{ Weight variation} = \frac{W - W1}{W1} \times 100$$

Where W is the weight of each tablet taken from the brand and W1 is the average weight of tablets from the brand. The thickness, diameter and hardness for each tablet then measured. The mean values, standard deviation and the relative error were calculated with the software instilled with the device.

Fig 2.1. Combination tester- ERWEKA/ Germany

2.2.2. Disintegration test on Clopidogrel tablets 75mg:

The disintegration time for six tablets from each brand was determined, using a disintegration tester (ERWEKA ZT320/ Germany) as seen in Fig 2.2. The time taken for tablets to disintegrate in distilled water at 37±0.5Cº until no particle remained on the basket of the system and all the granules to go through the wire mesh.

Fig 2.2. Disintegration tester- ERWEKA ZT320/ Germany

2.2.3. Dissolution test on Clopidogrel tablets 75mg:

The dissolution apparatus used was a six-station system with suitable glassware.

Instrument name: Dissolution tester- ERWEKA/ Germany (Fig 2.3).

Hydrochloric acid buffer pH 2

Apparatus 2: 50 rpm

Time: 30 minutes

UV Absorbance: 240 nm

USP reference standard information:

Name: Clopidogrel bisulphate 125mg

For use with specified USP compendia tester

Place of manufacturer: Rockville, MD: U.S.

Lot No: G1K326

Fig 2.3. Dissolution tester- ERWEKA/ Germany

The dissolution apparatus was set up using the UV spectrophotometer- SPECORD-analyticjena/ Germany, the puddles were lowered into the medium which consisted of one litter of 0.2M hydrochloric acid buffer pH 2.

2.3. Statistical analysis

Statistical analysis was computerized using the Statistical Program for Social Sciences (SPSS version 21) and Epi Info program was used to calculate the sample size. Descriptive statistics were used and all results are presented as frequencies, means ± standard deviation and percentages. The categorical data was compared using the Chi-square test and independent sample T test. A P-value of less than or equal to 0.05 was considered statistically significant. To assess the internal consistency, the item-to-total correlation and the reliability of the scale was evaluated through the use of standards statistical procedure described by Cronbach.

Chapter - 3

RESULTS

3. RESULTS

3.1. Adherence

A total of 200 patients treated with Clopidogrel were included in the study. Their mean ages were 63±10 years, more than half of the sample pooled (60%) were male. Almost all females were not working (94%), on the other hand half of males were either retired (51%) or working (49%). Patients' treatment period were classified into two stages. These stages were, patients treated for less than one year and others treated for more than one year. (Table 3.1)

Table 3.1. Characteristics of the studied population by percentage

Patients included in the study		200
Male 120 (60%)	Employed	59 (49%)
	Unemployed	0 (0%)
	Retired	61 (51%)
Female 80 (40%)	Employed	3 (4%)
	Unmployed	75 (94%)
	Retired	2 (3%)
Patients' ages	Mean ages	63±10 years
	Minimum	34 years
	Maximum	90 years
Patients on Plavix®	For less than one year	58 (65%)
	For more than one year	32 (36%)
Patients on different brands of Clopidogrel	For less than one year	42 (38%)
	For more than one year	68 (62%)

More than half of the patients on Plavix® and Apo- clopidogrel had high adherence towards their treatment (59% and 56% respectively). In contrast, about 72% of patients on other brands of Clopidogril had low to medium adherence as demonstrated in Figure 3.1.

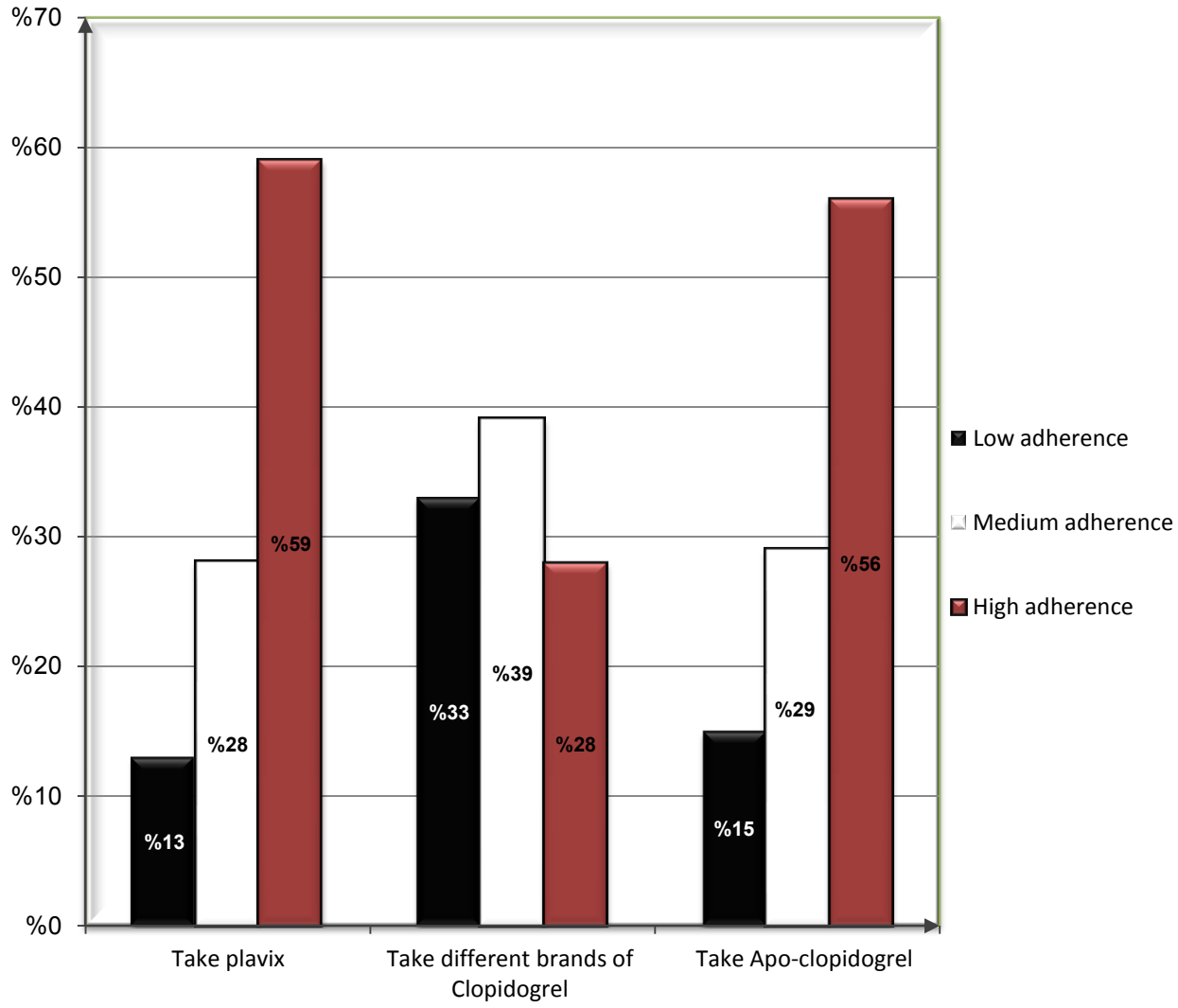


Figure 3.1. Adherence of patients treated with different brands of Clopidogrel tablets

There is a statistically significant relationship (p=0.05) between patients' adherence behaviour and their gender as represented in figure 3.2. Males have higher adherence (53%) toward their medication than females (36%). In addition, the percentage of females who have low to medium adherence was higher (64%) compared to the males (47%).

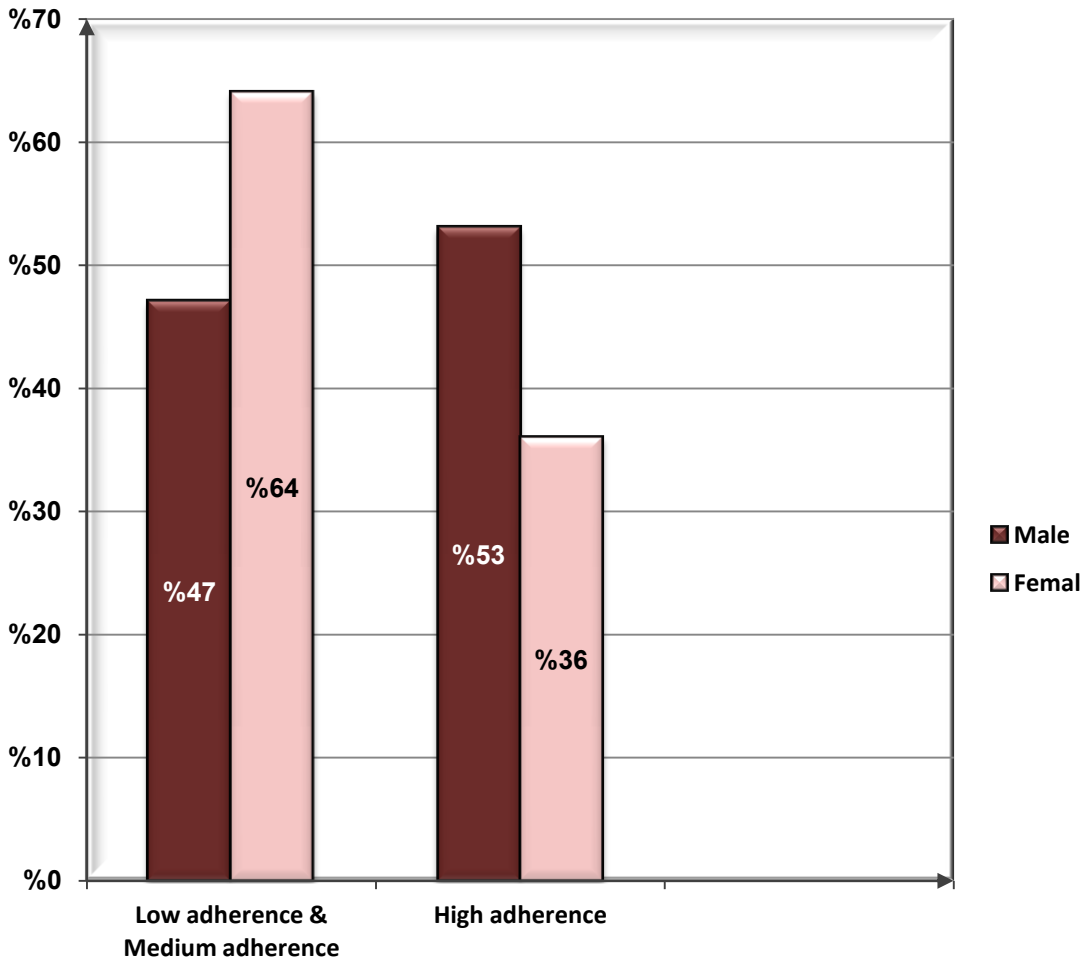


Figure 3.2. Adherence behaviour by gender

Non-adherence behavior frequencies varied across items, with the most respondents (46%) indicating “feel hassled by treatment plan” and the fewest respondents (4%) indicating that the “stopped taking medication when feeling worse” as shown in Figure 3.3.

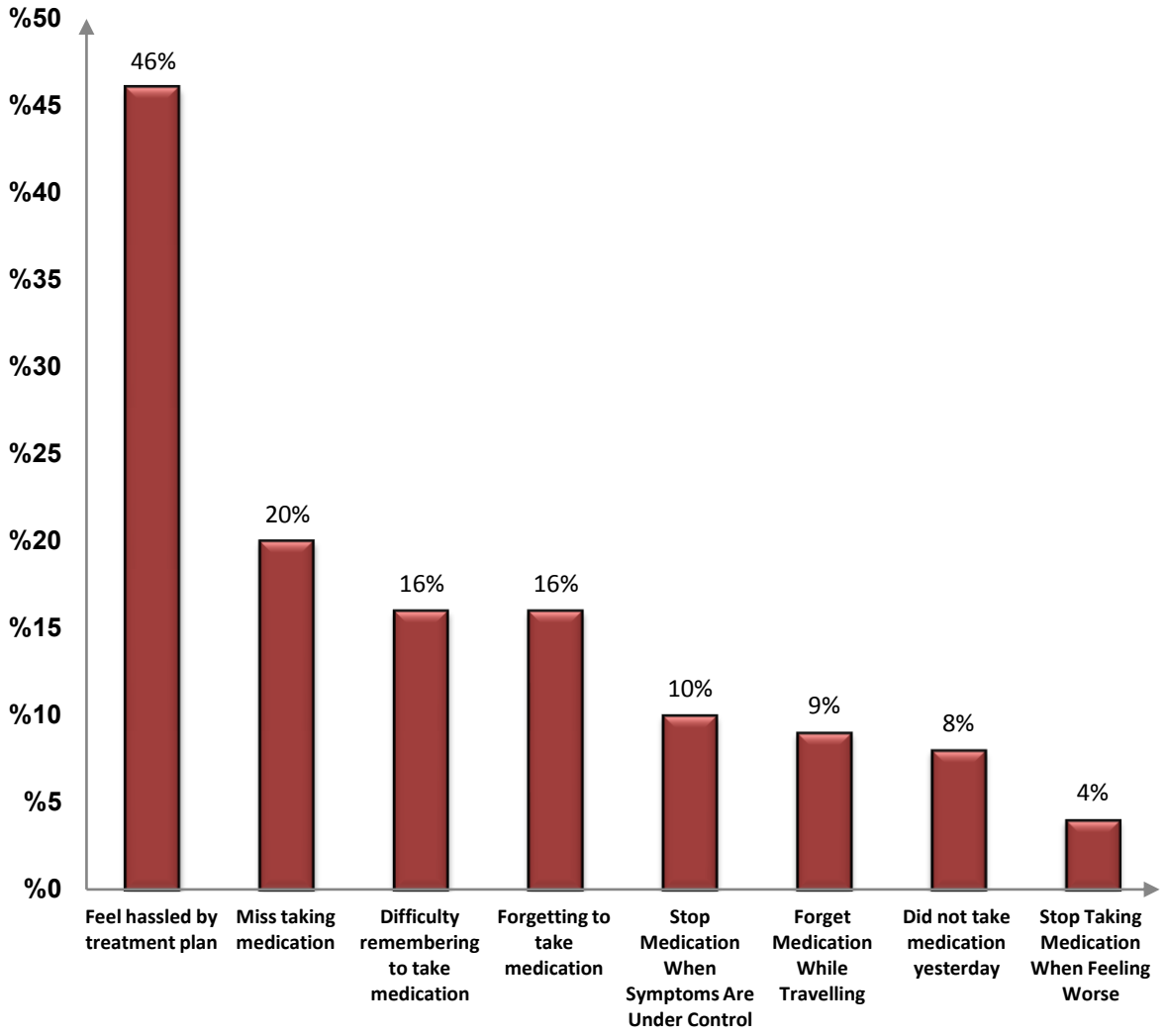


Figure 3.3. Non-adherent behaviors of patients on Clopidogrel tablets

Table 3.2 provides information about the item-to-total correlations. It presents which items explain more of the total variability, with 'Stop taking medication when feeling worse' having the lowest correlation and falling into the small effect size range and therefore reflecting a measure that deviates from the other items.

Table 3.2. Item-to-total correlations

Point Biserial with Total Score	Values
Forgetting to take medication	0.59
Difficulty remembering to take medication	0.64
Miss taking medication	0.65
Feel hassled by treatment plan	0.40
Forget medication while travelling	0.31
Stop medication when symptoms are under control	0.46
Stop taking medication when feeling worse	0.29
Did not take medication yesterday	0.34

If the correlation standards less than 0.3, this means the question is not related to the other items.

Table 3.3 provides estimates of the overall reliability of the MMAS (Cronbach's alpha = 0.755), as well as reliability in the absence of individual items. Reliability was reduced slightly with the exclusion of all items except "feel hassled by treatment plan," which has slightly improved the overall reliability.

Table 3.3. Alpha reliability estimates

Cronbach's Alpha	Values
All items	0.755
Excluding forget medication	0.703
Excluding missed medication	0.687
Excluding difficulty remembering to take medication	0.691
Excluding forget medication while travelling	0.751
Excluding feel hassled by treatment plan	0.756
Excluding stop taking when symptoms under control	0.729
Excluding stopped medication when feeling worse	0.754
Excluding did not take medication yesterday	0.746

3.2. Physical quality control tests

All quality control testes (Weight variation, Thickness, Hardness, Disintegration and Dissolution) for all samples were carried out according to United States Pharmacopeia [USP31, 2008].

Samples were film coated tablets and they found to vary in shape between the brands but most of them were circular with concave faces with pink Colour, except Antiplex® was long and ovate. The %weight deviation for all the brands complies with the official USP test specification, no more than 2 tablets outside the limit of (+/-) 5% and no tablet by more than 2 times the limit (table 3.4).

The tablets meet the USP specification of thickness test if no tablet outside the limit of (+/-5%). As seen in table 3.5, all brands pass the USP requirement except Antiplex® Dar Aldawa (Jordan).

Since Clopidogrel is a coated tablet, a force of 10-20 kilogram (98- 196 N) is considered the minimum requirement for tablet hardness. All brands pass the USP specification except Antiplex® by only one tablet; the test should be repeated on another ten tablets but because of restriction to get more samples, it has not completed (table 3.6).

All brands comply with the limit of USP disintegration test: the tablets must disintegrate within the times not exceeding 30 minutes (table 3.7).

The dissolution test results of the Clopidogrel film-coated tablets in buffer solution of pH 2 at 37 C° for the different brands are shown in table 3.8. The tolerance limit according to the USP pharmacopeia is not less than 80% of the labelled amount of Clopidogrel is dissolved in 30 minutes. The results clearly indicate that the dissolution profile for all brands except Antiplex®; complies with the release standards set for this products. The results are represented graphically in figure 3.4.

There is no significant difference between the brands of Clopidogrel and the innovator Plavix® in most of the cases. The results for the thickness disintegration of Antiplex®, thickness of Plavix®/ Turkey and hardness of Clopidogrel/ Ireland were significantly different in comparing with the innovator Plavix®/ France.

Table 3.4. %weight variation of Clopidogrel brands

Sample No.	% Weight deviation of Clopidogrel brands				
	Plavix® Sanofi Aventis (France)	Plavix® Sanofi Aventis (Turkey)	Clopidogrel® Clonmel Healthcare (Ireland)	Clopidogrel® Actavis (Iceland)	Antiplex® Dar Aldawa (Jordan)
1	-0.894	1.246	-1.128	-0.177	-1.897
2	-0.191	0.664	-0.125	0.671	0.901
3	0.472	0.741	-2.667	-0.495	0.792
4	-1.869	-0.811	5.71	1.201	0.956
5	-1.323	-2.053	-0.448	-0.247	0.937
6	0.121	-2.053	0.627	-1.06	-1.134
7	1.682	1.207	-5.28	0.671	-0.952
8	0.238	-0.151	0.09	-0.353	0.665
9	1.604	-3.178	1.736	-0.813	0.156
10	0.16	4.389	1.486	0.601	-0.425

Table 3.5. Thickness of Clopidogrel brands

Sample No.	Thickness by (mm) of Clopidogrel brands				
	Plavix® Sanofi Aventis (France)	Plavix® Sanofi Aventis (Turkey)	Clopidogrel® Clonmel Healthcare (Ireland)	Clopidogrel® Actavis (Iceland)	Antiplex® Dar Aldawa (Jordan)
1	3.99	4.02	4.61	4.3	5.7
2	3.98	4.02	4.64	4.33	5.83
3	4.01	4.04	4.58	4.3	5.86
4	3.94	3.95	4.79	4.34	5.83
5	3.95	3.95	4.66	4.29	5.82
6	3.99	3.94	4.63	4.26	5.81
7	4.03	4.03	4.52	4.35	5.81
8	4.01	4.0	4.65	4.27	5.76
9	4.04	3.9	4.65	4.29	15.41
10	3.99	4.1	4.7	4.3	15.53

Table 3.6. Hardness of Clopidogrel brands

Sample No.	Hardness (N) of Clopidogrel brands				
	Plavix® Sanofi Aventis (France)	Plavix® Sanofi Aventis (Turkey)	Clopidogrel® Clonmel Healthcare (Ireland)	Clopidogrel® Actavis (Iceland)	Antiplex® Dar Aldawa (Jordan)
1	128.0	139.0	137.0	139.0	176.0
2	121.0	134.0	144.0	144.0	184.0
3	136.0	125.0	124.0	147.0	174.0
4	131.0	130.0	168.0	148.0	120.0
5	121.0	121.0	136.0	142.0	192.0
6	125.0	124.0	159.0	146.0	182.0
7	130.0	139.0	127.0	134.0	175.0
8	123.0	135.0	150.0	154.0	213.0
9	137.0	121.0	157.0	140.0	186.0
10	134.0	136.0	149.0	147.0	164.0

Table 3.7. Disintegration time of Clopidogrel brands

Sample No.	Disintegration Time (min:sec) of Clopidogrel brands				
	Plavix® Sanofi Aventis (France)	Plavix® Sanofi Aventis (Turkey)	Clopidogrel® Clonmel Healthcare (Ireland)	Clopidogrel® Actavis (Iceland)	Antiplex® Dar Aldawa (Jordan)
1	9:19	10:08	8:5	8:13	1:09
2	9:19	9:4	8:5	8:27	1:09
3	10:3	9:42	8:5	8:13	1:09
4	9:3	10:08	8:5	8:13	1:09
5	9:3	10:08	9:14	8:27	1:09
6	9:58	10:08	8:5	8:13	1:09

Table 3.8. Dissolution results of Clopidogrel brands

Sample No.	% Q of Clopidogrel dissolve in 30 min. of Clopidogrel brands				
	Plavix® Sanofi Aventis (France)	Plavix® Sanofi Aventis (Turkey)	Clopidogrel® Clonmel Healthcare (Ireland)	Clopidogre® Actavis (Iceland)	Antiplex® Dar Aldawa (Jordan)
1	83.24	80.38	76.64	94.45	77.13
2	79.89	80.26	86.7	94.18	77.14
3	96.45	90.19	81.28	96.35	75.86
4	80.06	84.15	85.13	97.05	76.92
5	83.24	81.22	86.65	98.58	79.38
6	81.07	79.92	81.37	97.59	78.06
Average	**83.99**	**82.69**	**82.96**	**96.37**	**77. 42**

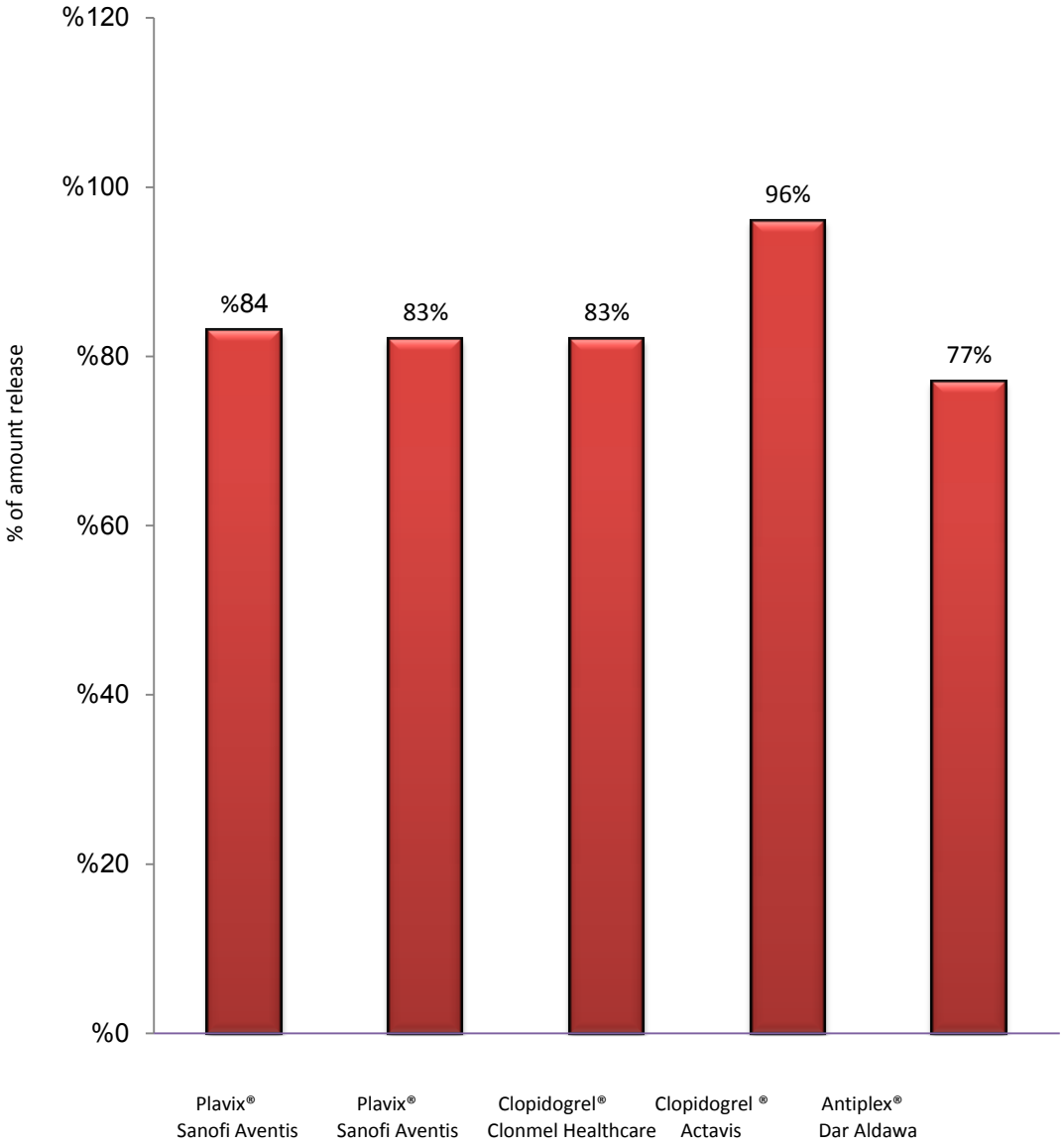


Figure 3.4. Mean % Q of Clopidogrel brands dissolve in 30 min.

Chapter - 4

DISCUSSION

4. DISCUSSION

Non-adherence to medications is considered one of the largest drug related issues. World Health Organization (WHO) states that non-adherence to medications is a "worldwide problem of striking magnitude" [5].

The main goal of this study was to evaluate the relationship between patient noncompliance and medications satisfaction of Clopidogrel by evaluating patients' adherence, followed by analytical evaluation of different Clopidogrel brands to investigate the arguments of physicians on these brands. In this study only Clopidogrel was selected from antiplatelet medications because of a high cost of these medications and restriction of the study time.

This study was the first systematically translate and validate the eight-item MMAS in Libya. Our study among Libyan patients on Clopidogrel treatment showed that the eight-item MMAS had a good reliability. In addition, the exclusion of "feel hassled by treatment plan" improved the overall reliability slightly. The results of this study reflect results of other studies that were carried out by Sakthong *et al* [40], Södergård *et al* [41], Al-Qazaz *et al* [42], Fialko *et al* [43], Roth and Ivey [44], Krapek *et al* [45], and the original eight-item MMAS study by Morisky *et al* [27], The highlighted studies found that the scale was reliable with a good predictive validity.

MMAS-8 has adequate psychometric properties for evaluating non-adherence in patients with cardiovascular diseases [46]. The reliability of the 8-item MMAS in our study was satisfactory (alpha= 0.755). This coefficient is lower than the 0.83 of the original 8-item MMAS [27, 25], but higher than that of other non-English versions, the French version (0.54) [47], the Thai version (0.61) [40], and the Malay version (0.67) [48, 42].

Our study results showed that patients use Plavix and Apo-clopidogril had higher adherence when compared to other examined brands of Clopidogril. This might be due to the believes that Libyan physicians prefer to prescribe those medications rather than the other brands. Also, Libyan patients believe that Plavix and Apo-clopidogril have better response than the other brands.

Ninety four percent of females tested were unemployed; this factor may explain why adherence to the treatment was more prevalent in males. The high cost of the innovator

drug and patients' budget may have played an important role [49]. Other factors associated with low adherence scores in women but not men include dissatisfaction with communication with their healthcare providers [50]. The poor medication adherence may result in increased health care cost; 33% to 69% of drug-related hospital admissions in US are consequence of poor medication adherence, along with a cost of about $100 billion a year [22].

Few data are available on factors associated with low adherence or early Clopidogrel discontinuation after percutaneous coronary intervention (PCI) [51, 52]. However, Prior use of clopidogrel, comorbid conditions such as diabetes and chronic pulmonary disease, prior hospitalization, PCI without stenting, and younger age had a negative impact on clopidogrel adherence [42, 53, and 54]. Our two factors are consistent with those found in the MMAS, categorized as intentional and unintentional [55, 56]. Items belonging to intentional factors are 'cutting back doses' and 'not taking medication'. When patients answered 'yes' for these items, health care providers should offer proper advice on medication administration [48].

In contrast, items belonging to unintentional factors are 'forgetting' and 'difficulty remembering to take medication'. Two exceptions were items 5 and 7. Item 5 'taking medication yesterday', was originally an unintentional factor, but the present participants used it as an intentional factor. They might have decided this based on the expected benefits of medication [57]. Conversely, item 7 'Feeling hassled about sticking to treatment plan' was originally an intentional factor, but the participants used it as an unintentional item and also it is considered one of the Patient-centered factors. If the patients do not follow or adhere to the treatment plan faithfully, the intended beneficial effects of even the most carefully and scientifically-based treatment plan will not be realized. The above examples illustrate the extent of the problem of therapeutic non-compliance and why it should be a concern to all healthcare providers [16].

Among the eight items, "feel hassled by treatment plan" (item 7) was the least adhered in our study. This could be a consequence of cognitive function deterioration, which interferes with the ability to remember to take medication. Vulnerability due to the long nature of managing and the cost of treatment could also have prevented patients' from taking their medication [57]. A study conducted in Taiwan mentioned that the Taiwanese population was the most at risk of non-adherence are those who perceived lower susceptibility to specific diseases and had been diagnosed with hypertension for a

longer time [58]. A study in Jordan showed that patients were highly adherent to their medication; however, it also highlighted that depression was associated with medication non-adherence [59], and a study done on patients who were prescribed statins, they find that patient-related predictors account for the largest incremental explanatory power in predicting adherence [60].

patients tended to stop taking medication based on how they felt [56]. The results of the study carried by Stavropoulou (2011) confirm the importance of patients leaving the consultation feeling well informed about their medication as this improves adherence. It also showed that the use of the Internet and the Media can be beneficial for adherence felt [61].

All brands used in the physical quality control tests of this work were within their shelf life as the time of the study. The four different generic alternatives of Plavix® tablets and the innovator brand were obtained from the retail private pharmacy within Tripoli city- Libya. The assessments of tablets involved qualitative and quantitative methods of evaluation. The qualitative methods of evaluation included tablet description, color, size and shape which were carried out by visual observation while quantitative evaluations used are weight deviation, thickness, hardness, disintegration and dissolution. A compressed tablets shape and dimensions are determined by the tooling during the compression process. The tested brands tablets were pink and their qualitative measures were acceptable comparing with the innovator drug. Colour consistency and a smooth texture are important for their easy identification and consumer acceptance. Therefore, colour and texture should be uniform throughout the tablet and from tablet to tablet.

A tablet designed to contain a specific amount of drug in a specific amount of tablet formula. The weight of the tablet being made is routinely measured to help ensure that a tablet contains the proper amount of drug. It is desirable that all the tablets of a particular batch should be uniform in weight. If any weight variation is there, that should fall within the prescribed limits. The weight variation test would be a satisfactory method of determining the drug content uniformity of tablets. The test is considered correct if not more than two tablets fall outside the range of (+/-) 5% and no tablet by more than two times the limit. The difference of weight variation in tablets can lead to variation in doses. The uniformity of weight determination for all the brands showed compliance with the official specifications as non of the brands deviated from

their mean. This indicates that the weights of each brand tablet are within the expected official specifications.

Thickness and diameter are non-pharmacopoeial requirements but naturally it will have an effect on packaging for uniformity of diameter of tablets the requirements apply to the tablets which are not sugar coated, enteric-coated or film coated. A deviation of ±5% from the stated diameter is allowed except that for diameters exceeding 12.5mm the deviation allowed is ±3%. The thickness and diameter of a tablet can vary without any change in weights.

Tablet requires a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging and shipping. In addition, tablet should be able to withstand reasonable abuse when in the hands of consumer. Adequate tablet hardness and resistance to powdering are requisite for customer acceptance. More recently, the relationship of hardness of tablet disintegration and perhaps more significantly, to drug dissolution release rate, has become apparent. According to The British Pharmacopoeia (2008) a maximum loss of weight not greater than 1% is considered acceptable.

The present USP and national formulary (NF) of United Sate disintegration tests measure only the physical break-up of the tablet, which may not necessarily correlate with drug bioavailability. In order for a drug to be absorbed, it must be present in a solution form. It is possible that the particles from the disintegrated tablets might not further disintegrate or dissolve and thus no bioavailability assurance can be obtained from formulations meeting only the official disintegration tests.

After comparing four brands of Clopidogrel tablets to the innovator drug product Plavix® for weight variation, thickness, hardness and dissolution; the results clearly indicate that all brands comply with the pharmacopeia standards set for these products except Antiplex® tablets which failed in thickness, hardness and dissolution tests.

Results could be explained by the variation in some testing results of tablets due to variation in the excipients used by each manufacturer. This is generally due to the difference of density of granules, pressure applied for compression, the speed of compression, the die and punch selected for making the tablets.

This indicates that all brands of the Clopidogrel that passed the pharmacopeia standards are presumably suitable for the In-vivo performance. Antiplex® is not of equivalent quality compared to the innovator drug product.

In order to characterize different brands quantitatively and qualitatively, they were further compared with the innovator drug. The physical appearance of tablets showed that all brands of Clopidogrel have the same colour as the innovator Plavix®. The colour of tablets usually affects the compliance of patient. Comparison of the shape of tablets for different brands to the shape of innovator brand indicated matching with the innovator brand shape except for Antiplex®. The shape of the tablets are adjusted by the design of the tablet machine and usually used as character of the manufacturer.

The results of both parts of our study (adherence and quality control tests) indicate that the cost does not reflect the quality or effect of the product.

As practice of clinical pharmacy aims to help maximize drug efficacy, minimize drug toxicity and promote cost-effectiveness; in order to achieve this, pharmacists require to work as fully integrated members of the health care team.

Both as team members and members of their own professional body [62], pharmacists should enforce the physician to prescribe other brands of Clopidogrel with same efficiency.

Chapter - 5

CONCLUSIONS

5.1. CONCLUSIONS

Adherence to the innovator Plavix® plays an important role in increasing the efficacy of the drug when comparing it to other generic alternatives. Patients on different brands of Clopidogrel "who had been described by physicians in having low medication efficacy" reported low medication adherence. The quality analysis tests reinforce the previous findings that most of the alternatives were similar compared to the innovator drug product. The study also showed that the 8-item MMAS was demonstrated to have good validity and reliability. Given the humanistic and economic burden associated with non-adherence, it is especially important to have reliable, inexpensive, easily accessible means (such as MMAS-8) in adherence assessment. It is also mandatory for manufacturers and all other key players in the drug distribution business and Center for Food and Drug Control/ Tripoli to assure that final products reach consumers with high quality and efficacy. This is only possible in an environment of high ethical and moral standards.

5.2. FUTURE WORK

Further study is needed in order to be able to separate the R-enantiomer of Clopidogrel, by an enantiospecific liquid chromatographic method to determine the impurities.

And, to compare the bioequivalence of alternatives to the innovator drug product (PLAVIX ®) by In-Vivo In-Vitro Correlation (IVIVC) method.

Chapter - 6

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6. REFERENCES

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APPENDIX:

The questionnaire used to collect data related to the patient adherence

الإسم (إختياري):..... العمر:.....
الجنس:..... الوظيفة:..... التاريخ:.....
الاسم التجاري للدواء المستخدم:.....

**** يرجى الإجابة عن الأسئلة بنعم أو لا**

هل تنسى في بعض الأحيان تناول دوائك؟ نعم/لا
الناس أحيانا يفوتهم أخذ أدويتهم لأسباب غير النسيان. فكر على مدى الأسبوعين الماضيين، هل هناك أيام لم تأخذ خلالها الدواء؟ نعم/لا
هل سبق لك أن توقفت عن تناول دوائك أو انقطعت عنه دون إبلاغ طبيبك لأنك شعرت بأنك أسوأ عند تناوله؟ نعم/لا
عند السفر أو مغادرة المنزل، هل تنسى في بعض الأحيان أخذ الدواء معك؟ نعم/لا
هل أخذت كل دوائك بالأمس؟ نعم/لا
عندما تشعر بأن الأعراض الخاصة بمرضك تحت السيطرة، هل تتوقف أحيانا عن أخذ الدواء؟ نعم/لا
أخذ الدواء كل يوم هو إزعاج حقيقي بالنسبة لبعض الناس. فهل شعرت في بعض الأحيان بالانزعاج لتطبيق خطة العلاج الخاصة بك؟ نعم/لا
هل هناك صعوبة لديك في تذكر اخذ الدواء عادة ؟ (يرجى اختيار الإجابة المناسبة) أ. أبداً / نادراً ب. مرة واحدة في بعض الأوقات ت. أحياناً ث. عادة ج. كل الأوقات

رقم الهاتف:	توقيع المريض:

الملخص

التزام المرضى بأنظمة الرعاية الصحية الخاصة بهم أمر مهم للوصول إلى أفضل النتائج الصحية. و مع ذلك، قد أعطي القليل من الاهتمام لتقييم الخصائص السيكولوجية لقياس هذا الالتزام في المجتمع الليبي.

تهدف الدراسة لإجراء عمل شامل لتقييم العلاقة بين عدم إلتزام المرضى الذين يتناولون الكلوبيدوجريل وإعطاء فعالية مُرضية للأدوية وذالك لتحري حجة الأطباء الليبيين. كذلك وصف جودة 4 أصناف من الكلوبيدوجريل و مقارنتها بالمنتج المبتكر البلافيكس لغرض دعم البحث.

تم إختبار مدى إلتزام المرضى على مجموعة علامات تجارية لعقار الكلوبيدوجريل المتوفرة في الأسواق الليبية بواسطة مقياس موريسكي للإلتزام الدوائي ذو 8- بنود. و تمت مقارنة 4 بدائل عامة للكلوبيدوجريل بالمنتج المبتكر من حيث إختلاف الوزن، السمك، الصلابة، التفكك و إنحلال.

تم إختيار المرضى الذين يتناولون العلامات التجارية المختلفة لعقار الكلوبيدوجريل بشكل عشوائي (ن = 200)، متوسط أعمار عينة الدراسة (63 ± 10) عاما. تم إنجاز مقابلة شخصية مع المشاركون من مختلف مستشفيات مدينة طرابلس بمساعدة إستبيان. كان الاستبيان المستخدم هو مقياس موريسكي للإلتزام الدوائي (MMAS-8). تم تقييم صحة و دقة الإستبيان. وجدت الدراسة أن أكثر من نصف المرضى الذين يتناولون البلافيكس و الأبو-كلوبيدوجريل علي مستوى عالي من الالتزام 59٪، 56٪ على التوالي. في حين حوالي 72٪ من المرضى على علامات تجارية أخرى من عقار الكلوبيدوجريل سجلوا مستوي منخفض إلى متوسط من الالتزام. و أظهرت دراستنا أن البنود الثمانية لمقياس مورويسكي له دقة جيدة (ألفا كرونباق = 0.755). بالإضافة إلى ذلك، فإن إستبعاد بند "يشعر مستأ من خطة العلاج" يحسن دقة البنود قليلا (46٪ يظهر "يشعر مستأ من خطة العلاج"). يوجد علاقة ذات دلالة إحصائية (ع = 0.05) بين سلوك إلتزام المرضى و جنسهم. و وجدت الدراسة أن الذكور لهم إلتزام دوائي عالي نحو أخذ أدويتهم مقارنة مع الإناث (53٪، 36٪ على التوالي).

تشير النتائج بشكل واضح بأن الأصناف الأربعة لأقراص الكلوبيدوجريل تمتثل إلى معايير دستور الأدوية الموضوعة لهذه المنتجات إختلاف الوزن، السمك، الصلابة، التفكك و إنحلال ماعدا أقراص الأنتيبليكس حيث أخفقت في إختبارات السمك، الصلابة، و إنحلال.

تستخلص الدراسة أن المرضى الذين يتناولون العلامات التجارية المختلفة لعقار الكلوبيدوجريل "الذين وصفوا من قبل الأطباء بأن لديهم فعالية دوائية منخفضة" قدموا التزام دوائي منخفض. اختبارات الرقابة النوعية تعزز النتائج السابقة. هذا يثبت لماذا المنتج المبتكر البلافيكس هو الأكثر فعالية مقارنة بالبدائل العامة التجارية الأخرى له. كذلك من الضروري للمصنعين وجميع ذوي الشأن الآخرين في مجال توزيع الأدوية التأكد من أن المنتجات النهائية تصل إلى المستهلكين بجودة وفعالية عالية. هذا غير ممكن إلا في بيئة من المعايير الأخلاقية الأدبية العالية.

جامعة طرابلس

كلية الصيدلة

قسم الصيدلانيات

طرابلس- ليبيا

توقع الالتزام الدوائي باستخدام مقياس موريسكي للالتزام الدوائي و تقييم تحليلي لأدوية مضادات الصفائح المتوفرة في ليبيا

مقدمة من

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