Republic of Yemen
Ministry of Higher Education and
Scientific Research
Emirates International University
Faculty of Medicine and Health Sciences
Department of Pharm.D

Evaluation of Secondary Prevention Medications among Patients with Acute Coronary Syndrome in Sana'a City, Yemen

A graduation research project submitted as partial fulfillment for the requirements of the bachelor's degree in Pharm.D

Research Team

Salah Aldeen Mansour Ali Ahmed
Ali Ahmed Ali Almatar
Emad Saleh Naji Abraham
Muhammad Sadiq Abdul Wahab
Mohssen Mohammed Qaid Alased
Haifa'a Mohammed Naji AL-hadhrie
Jihan Saeed Mohsen Alsabry
Monya Najeeb Mohammed Rashed
Ebrahim Abdalbari Ahmed Algarm
Alaa Abdul Rahman Hammoud Zaid

Under the Supervision of

Assist.Prof. Dr. Moktar Abdul Hafiz Al-Ghorafi

Head of Pharm.D department, EIU.

Dr. Abdullah Saleh Ahmed Saadallah

Master in Clinical Pharmacy

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(سورة التوبة آيه ١٠٥)

Dedication

We dedicate this research to Yemen, our beloved country , Which we will always and forever remain in its protection and do everything we can to advance and improve it. To our families whom surround us with their prayers as a constant shadow and support us all the time. To our lifetime in years that occurred between effort, tiredness, the sting of science and research , the hardness of war and the fight with life. Also we dedicate this work to everyone who enlightened the mind of others with his knowledge or guided the correct answer to the bewilderment of his questioners and everyone who believed in the good word and worked for it.

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List of abbreviation

ACS	Acute coronary syndrome
ACEI	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blockers
ACC/AHA	American college of cardiology/American heart association
CHD	Coronary heart disease
CAD	Coronary artery disease
CABG	coronary artery bypass graft
IHD	Ischemic heart disease
HDL	High density lipoprotein
HF	Heart failure
HTN	Hypertension
DM	Diabetes
DAPT	Dual Anti platelet Therapy
LDL	Low density lipoprotein
PCI	Percutaneous primary intervention
TIMI	Thrombolysis In Myocardial Infarction
STEMI	ST-segment elevation MI
SL NTG	sublingual nitroglycerin
r-PA	Retaplase
NSTE-ACS	non–ST-segment elevation
ECG	Electrocardiogram
HEART	History, ECG, Age, Risk factors, and Troponin
GRACE	Global Registry of Acute Coronary Events
BNP	B-type natriuretic peptide
UA	Unstable angina

Abstract

Background: Five-medication regimen is recommended for patients after acute coronary syndrome (ACS) as a secondary prevention strategy at discharge to reduce recurrence and improve mortality.

Objective: This study aimed to assess the appropriateness of ACS secondary prevention among patients with ACS in Yemen.

Methods: A retrospective cross-sectional study was performed at three tertiary hospitals in Sana'a, Yemen in the period from January 2020 to December 2021. Data were collected from patient's medical files. Appropriate ACS secondary prevention is defined as a combination of five medications; aspirin and clopidogrel, statins, beta-blockers (BBs), and angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs). Association between appropriate secondary prevention of ACS and other variables was studied using chi-square test. Univariable and Multivariable logistic regression were also studied to determine the extent of association between the appropriateness of secondary prevention of ACS and different variables.

Results: A total of 775 patients' medical file were reviewed, of them 669 patients were included in the final analysis. The majority (74.4%, n= 498) of patients were between 18 to 64 years, and 78.2% (n=523) of patients were male. Most patients (65.6%, n=439) were diagnosed with ST-segment elevation myocardial infarction, followed by none ST-segment elevation myocardial infarction (24.5% , n=164) and Unstable Angina (9.9%, n=66). Comorbidities were identified in 72.6% (n=486) of patients. Hypertension (48.3%, n=323) and Diabetes (44.7%, n=299) were the most common risk factors. About 98.5% (n=659) of patients were on aspirin, 95.1% (n=636) on clopidogrel, 94.3%(n=631) on dual antiplatelet therapy, 93.3% (n=624) on statins, 69.5%(n=465) on BBs, and 60.4% (n=404) on ACEIs/ARBs. Appropriately ACS secondary prevention using the five medication was 46.5% (n=311) of patients. The inappropriate ACS secondary prevention were significantly higher among patient with UA (OR = 2.44, P= 0.002), single patients (OR= 2.251, P= 0.017), and patients who were treated at private sectors (OR= 3.589, P= 0.000).

Conclusion: Appropriately ACS secondary prevention using the five guideline-recommended medications were suboptimal in Yemen. Certain factors, such as having UA, marital status , and health sector may have effect on the appropriate ACS secondary prevention.

Keywords: acute coronary syndrome, secondary prevention, appropriate ACS secondary prevention, Yemen.

Chapter one : Introduction

1. Introduction

1.1 Background

Cardiovascular disease (CVD) has become the foremost cause of death and permanent disability in western countries, and disability worldwide[1]. CVD is an umbrella term for various diseases affecting the heart and blood vessels. They include coronary artery disease (CAD), cerebrovascular disease and peripheral artery disease[2]. Acute coronary syndrome (ACS) is a subcategory of CAD. ACS is categorized into myocardial infarction (MI) (with ST-segment elevation or non-ST segment elevation) and unstable angina (UA)[3]. Both categories of ACS result in loss of oxygenated blood supply to the myocardium cells, causing cell necrosis and death. Therefore, ACS is a life threatening condition and the leading cause of death in both developed and developing countries[4]. Additionally, re-attack of ACS is common, particularly when the well-known risk factors of ACS are not properly controlled. Controlling the risk factors using certain medication, in order to prevent re-attack or recurrent ACS is called secondary prevention[5].

National guidelines recommend five medications to be used as secondary prevention, they include, aspirin, clopidogrel, beta blocker (BB), statin and angiotensin converting enzyme inhibitors ACEI/ angiotensin II receptor blockers ARB [6]. Regular and correct usage of secondary prevention medications increase the quality of life and lower the risk of repeated ischemic events and mortality for ACS patients[7]. However, several reports showed that, there is a wide gap between what is recommended and what is clinically practiced, including the type medications and their optimal dosage[2,5,6]. Moreover, there is no published study that evaluates the optimization of secondary prevention medications among Yemeni patients with ACS. Therefore, the current study aims to help fill the gap and assess the drugs used for secondary prevention for Yemeni patients with ACS during their discharge.

1.2 Pathophysiology

ACS results primarily from decreased myocardial blood flow secondary to a blockage or partially blockage coronary artery thrombus which formation from accumulation of atheromatous plaques within the walls of the arteries that supply the myocardium after decades of progression (Plaque buildup (fat, cholesterol, proteins, calcium, white blood cells) takes years to form in lumen) some of these atheromatous

plaques rupture or erosion, the thrombogenic contents of the plaque are exposed to blood elements that induce platelet adhesion and activation (formation of thrombosis on top of plaque), which promote the release of platelet-derived vasoactive substances (do vasoconstriction), both thrombus and vasoconstriction do acute phase of attack[5,6]. An injury that transects the entire thickness of the myocardial wall results in a STEMI which will result in the release of biomarkers, mainly troponins T or I, from the necrotic myocytes into the bloodstream. NSTEMI is limited to the subendocardial myocardium, and is usually smaller than a STEMI, resulting in lower mortality and complications. NSTEMI differs from UA in that ischemia is severe enough to result in the release of troponins[2,6].

1.3 Classification of ACS

Acute coronary syndromes (ACSs), including unstable angina (UA) and myocardial infarction (MI), are a form of coronary artery disease (CAD) that comprises the most common cause of CVD death. ACS is a spectrum of disease encompassing ST-segment elevation MI (STEMI) or non–ST-segment elevation (NSTE)-ACS, which are classified according to electrocardiogram (ECG) changes and underlying pathophysiology[8,9].

1.4 Etiology

The primary cause of coronary artery disease, atherosclerotic coronary artery plaques, is due to endothelial dysfunction, inflammation, and the development of fatty streaks (CAD)[5]. An acute coronary syndrome is brought on by coronary artery embolism (blockage by blood clot, air bubble, fat or other material), coronary artery spasm, or spontaneous coronary artery dissection[10].

1.5 Risk factors

Numerous risk factors (Figure 1) can result in the development of cardiovascular diseases . These variables can be broadly divided into two categories, namely risk factors that can be modified and risk factors that cannot be modified . Modifiable risk factors, such as obesity, blood lipids, and behavioral factors, are preventable contributors to cardiovascular disease. Risk variables that cannot be changed, such as age, gender, and genetic predisposition, are referred to as nonmodifiable risk factors. In both stages of secondary prevention, early detection and intervention, awareness of these risk variables is extremely important[3].

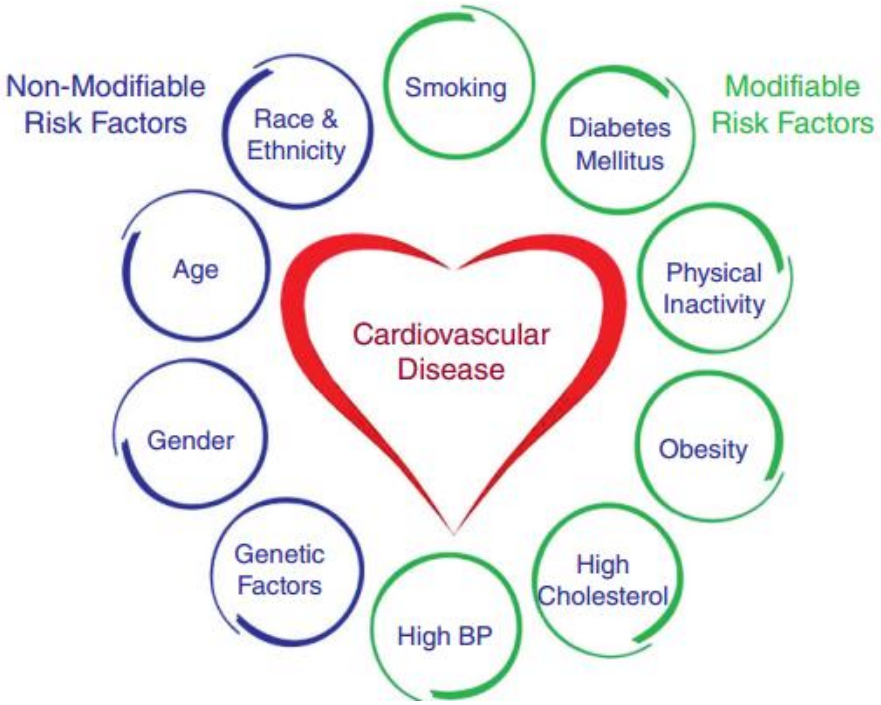

Figure 1: Cardiovascular risk factors [11]

1.6 Nonmodifiable risk factors

1.6.1 Age

The risk of having ACS increases with age ; around 80% of those who die from it are 65 or older . around 10 - 15 years earlier in life, men tend to develop it[3]. Even though they are younger, people have a lesser risk of developing CHD. In spite of this, younger people still experience worse clinical outcomes from ACS than older persons do[3,12].

1.6.2 Gender

For both genders, CVD remains one of the most common causes of mortality. Although males have a higher risk of developing coronary heart disease, whereas females are more likely to suffer from strokes and heart failure, according to research[3], recent studies show a considerable increase in the case fatality rates of ACS in females, while the mortality rate from CAD has decreased in males[12]. Also

statistical research finds that specific signs of ACS are more common in one gender relative to the other [3,12].

1.6.3 Genetic factors and Family history

The familial clustering of coronary artery disease (CAD) is well documented and likely results from a confluence of environmental factors, heritability of conventional risk factors, and specific predisposing genetic mechanisms. A positive FHx and a high GRS may predispose to acute coronary syndrome via accelerated atherosclerosis or other mechanisms [13].

1.6.4 Ethnicity

For groups with various ethnic backgrounds residing in the West, there are variances in CVD. For instance, in the United States of America, rates of ACS have been greater among African Americans than among other races, with the incidence among black women exceeding that among white men. Studies have revealed that certain minority groups in the USA have greater rates of classic CVD risk factors, varying rates of revascularization procedure treatment, and increased CVD morbidity and mortality[1].

1.7 Modifiable risk factors

1.7.1 Diabetes

Diabetes increases the risk of both atherosclerosis and ACS. Compared to people without diabetes, people with type 2 diabetes mellitus have a two- to six-fold increased risk of dying from cardiovascular causes. More than 25% of all new cardiovascular events in people with diabetes are related to the development of ACS or cardiovascular mortality [13].

1.7.2 Obesity

A condition known as obesity is one in which body fat builds up and poses health hazards. While several studies demonstrate that obese people have a comparatively increased risk of CVD, few demonstrate a causal link between weight/obesity and CVD. Numerous other risk variables, including blood pressure, hyperglycemia, and lipids (cholesterol), are linked to obesity[3].

1.7.3 Physical activity

It has been demonstrated that regular aerobic exercise can help with weight loss and blood pressure reduction. Physical inactivity is a significant risk factor for type 2 diabetes as well as an increased incidence of developing hypertension, a CHD risk factor . To lower cardiovascular risk and to aid in the prevention of diabetes, current national guidance suggests that adults engage in aerobic activity of at least 150 minutes of moderate intensity , 75 minutes of vigorous intensity , or a combination of moderate and vigorous intensities, along with muscle-strengthening exercises, every week [11,14] .

1.7.4 Hypertension

An increased blood pressure level has a particularly potent impact on stroke, and there is a clear correlation between hypertension and coronary heart disease. The Blood Pressure Lowering Treatment Trialists' Collaboration has investigated how blood pressure lowering affects mortality and the emergence of significant cardiovascular events. The summary looked at data from 29 randomized trials (n = 162 341 patients), and the main finding was that the more the blood pressure was lowered, the better. Therefore, decreasing blood pressure is crucial for both primary and secondary prevention of significant cardiovascular events, such as the emergence of ACS[2].

1.7.5 Lipid abnormalities

Reduced atherogenesis and a lower risk of cardiovascular disease are linked to lower levels of low-density lipoprotein (LDL) cholesterol. High HDL cholesterol levels are protective, but low HDL levels increase risk. Large-scale cholesterol-lowering trials have shown a decreased risk of cardiovascular events in those who received treatment but did not have evident coronary artery disease. The risk of major cardiovascular events was lowered by about one-third after three years of statin therapy[2].

1.7.6 Smoking

The hypothesis that tobacco use increases the risk of developing CAD is backed up by epidemiologic research. Despite the fact that the mechanisms underlying this effect are unclear , tobacco use has a negative impact on vascular biology . By influencing endothelial function, oxidative processes, platelet function, fibrinolysis,

inflammation, lipid oxidation, and vasomotor function, smoking promotes the development of both atherosclerosis and thrombi formation [1].

1.8 Risk stratification

Patients are classified as having a low , medium, or high risk of death, MI, or the possibility that their medication will fail and they will need immediate coronary angiography and PCI[14]. These factors include the patient' s symptoms, past medical history, ECG, and troponins.As soon as feasible, the patients who may benefit from a reperfusion strategy for STEMI or an early invasive or medicinal management approach for NSTEACS should get initial treatment based on risk classification.[2,6] For instance, STEMI patients that have the highest short-term mortality risk; as a result, rapid reperfusion treatments should be started. Patients with STEMI should be transported to a coronary critical care unit and further medication should be started in the ED if they are not eligible for reperfusion therapy . It is more difficult to risk-stratify a patient with NSTE-ACS since results can differ between UA and NSTEMI. Adverse cardiac events are more likely to occur in patients with a high likelihood of coronary ischemia, but not all patients who come with suspected NSTE-ACS have CAD.[14,22] Some people eventually receive diagnoses for nonobstructive CAD or microvascular illness as well as chest pain. Patients with NSTE-ACS, ST -segment depression, and/or increased troponin are generally more likely to die or have a new or recurrent MI[14].

When predicting the short- and long-term event rates of patients presenting with NSTE-ACS, a variety of risk assessments are available and should be used. These include the History, ECG, Age, Risk factors, and Troponin (HEART) score as well as the Thrombolysis in Myocardial Infarction (TIMI) risk score for NSTEACS and the Global Registry of Acute Coronary Events (GRACE) score. The risk of adverse cardiac events, such as death, new or recurrent MI, or the requirement for urgent revascularization, during the short term (2 to 6 weeks), increases linearly with higher scores. Depending on the risk assessment, a management strategy is chosen, and patients are either treated (1) using an early invasive strategy that involves coronary angiography in patients classified as high-risk of CV events based on clinical characteristics (e.g., high TIMI score 5-7), or (2) using an ischemia-guided strategy , where patients initially receive medication therapy only and will undergo an invasive evaluation if they fail medical therapy (e.g., continued ischemia despite occlusion) or

may show ischemia objectively on noninvasive stress testing. Patients classified as low-risk are typically the only ones who receive the ischemia-guided approach (eg, TIMI score 0–3). Typically ,patients with moderate to high risk are recommended for an invasive procedure called early coronary angiography[6,14].

1.9 Clinical Presentation and Diagnosis

1.9.1 Symptoms and Physical Examination Findings

The most typical time for severe new-onset or escalating substernal angina to occur at rest is for at least ten minutes.[6] The chest pain may not be present, in which case the pain may radiate to the shoulder, down the left arm, and to the back or jaw. Other signs include diarrhea, nausea, and shortness of breath.[6,15] Even though it resembles stable angina, the duration and intensity may be longer. Elderly, female, and diabetic patients may exhibit a more unusual presentation, which includes anginal equivalents of epigastric discomfort, unexplained shortness of breath, or indigestion in the absence of chest pain[16]. There are no "classic" physical signs that are unique to ACS. Patients with ACS may exhibit signs of acute HF, such as jugular vein enlargement, an S3 sound on auscultation, or pulmonary edema on a chest X-ray. Arrhythmias including tachycardia, bradycardia, or heart block may also be present in patients[6,15].

1.9.2 12-Lead ECG

A 12-lead ECG has specific characteristics that can help diagnose and risk-group a patient with an ACS. A 12-lead ECG should be obtained and read within 10 minutes of presentation to an ED with symptoms of ischemic chest pain. If the patient is still exhibiting symptoms and the doctor has a strong suspicion that the patient has ACS, more ECGs should be taken if the initial one is not diagnostic every 15 to 30 minutes during the first hour.[17] The time it takes for myocardial reperfusion to occur should be as short as possible, hence emergency medical system personnel should attempt to perform an ECG whenever possible.[22] If a previous ECG is available, it should be examined to determine whether any ischemia alterations are present, with new findings being more suggestive of an ACS. Key ECG abnormalities that point to myocardial ischemia or infarction include ST segment elevation (STE), ST segment depression, and T wave inversion (see Figure 2). The location of the coronary artery that is the source of the ischemia or infarction can be determined using alterations in the ST-segment and/or T-wave in specific groups of ECG leads.[2,6]

Furthermore, acute STEMI can be distinguished by the development of a new left bundle-branch block and chest pain. About one-third of individuals with MI have STE on their ECG, while the other two thirds have ST-segment depression, T-wave inversion, or, occasionally, no ECG abnormalities at all. The most recent recommendations state that a new STE in at least two contiguous leads of greater than or equal to 2 mm in men and greater than or equal to 1.5 mm in women in leads V2-V3 and/or of greater than or equal to 1 mm in other leads is diagnostic of STE, absent left bundle-branch block or left ventricular hypertrophy. Because some areas of the heart are more "electrically silent" than others, myocardial ischemia may not be seen on an ECG[17]. To ascertain the patient's likelihood of developing a new MI or other consequences, it is crucial to analyze the ECG results in conjunction with clinical symptoms, other risk factors for CHD, and biochemical indicators of myocardial necrosis such troponin I or T[6].

1.9.3 Biochemical Markers/Cardiac Enzymes

The diagnosis of MI needs to include biochemical indicators of myocardial cell loss.[17] Detection of a rise and/or fall of cardiac biomarkers with at least one value above the 99th percentile of the upper reference limit and with at least one of the following: (a) symptoms of ischemia; (b) ECG changes of new ischemia or development of pathological Q waves; (c) imaging evidence of new loss of viable myocardium; (d) new regional wall motion abnormality; or (e) identification of an intracoronary thrombus by angiography or autopsy as shown in (see Figure 2).[6]

According to the most recent recommendations, only the use of troponin tests is advised for determining myocardial necrosis.[15,17] Approximately 2 to 4 hours after a MI, troponins are released into the bloodstream, and they typically reach their peak between 18 and 24 hours later . Troponin levels may persist for up to two weeks. Since up to 15% of readings that were initially below the level of detection (a "negative" test) climb to the level of detection (a "positive" test) in subsequent hours, a single measurement of non-high-sensitivity troponin is insufficient to rule out a diagnosis of MI. A single "positive" troponin may also not be secondary to a MI because other clinical conditions that can elevate troponin levels include pulmonary embolism, tachyarrhythmias, pericarditis, myocarditis, and sepsis. These conditions can make the diagnosis more difficult. In patients with ACS, measuring N-terminal

pro B-type natriuretic peptide (BNP) may assist predict long-term mortality risk, but it does not help with acute diagnosis[6,17].

With the development of troponin I and troponin T, measurements can now be made well below the reference range' s 99th percentile. The "level of detection " refers to the lowest level that the test is capable of detecting. The diagnosis of MI can be ruled out if the first troponin T is below the level of detection, and no additional risk stratification is required. A second level at 1 to 6 hours should be collected and risk classification carried out for individuals presenting with troponin T above the level of detection but below the 99th percentile (see "Risk Stratification " section). The MI diagnosis can be confidently ruled out if there is no change between the second and first troponin T n levels. If the patient arrived at the hospital less than three hours after the onset of symptoms and the first two levels are above the level of detection but below the 99th percentile, a third level is advised. Any time a value exceeds the 99th percentile, MI is confirmed as a diagnosis[6,15,17].

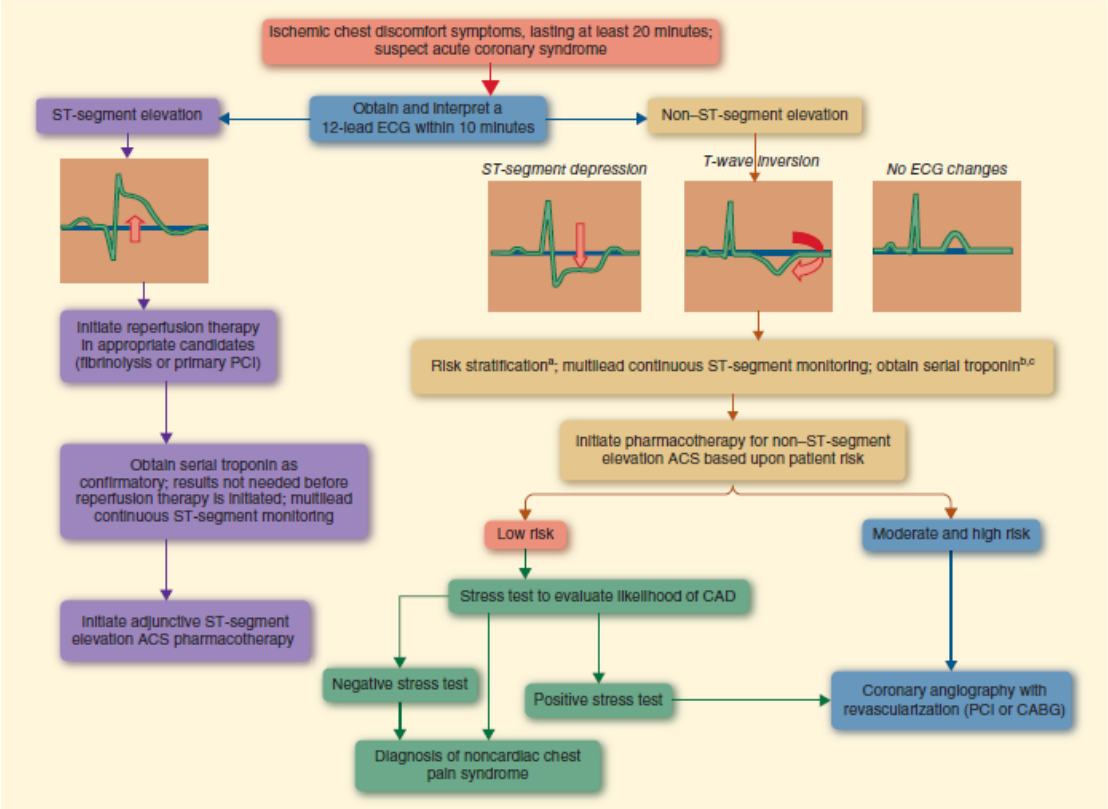

Figure 2: Evaluation of the acute coronary syndrome patient[6]

1.10 Complication

Patients with ACS, especially those with MI, may experience a variety of consequences, which might appear hours to weeks after the index event, depending on

the severity and location of the ischemia.[17] Electrophysiologic abnormalities, such as ventricular arrhythmias, bradyarrhythmias, and heart blocks, are possible and may happen either in the acute phase of the ischemia event due to electrical instability caused during myocyte destruction or in the recovery phase due to ventricular remodeling. Depending on the degree of myocardial necrosis and ensuing impairment of ventricular contractility , HF may be present. Cardiogenic shock, an immediate, severe form of HF linked to hypotension, systemic hypoperfusion, and poor prognosis, actually develops in 5% to 6% of STEMI patients. Within the first 10 days after infarction, myocardial rupture of the papillary muscle, ventricular septum, or free wall of the ventricle is conceivable as a result of significant myocyte necrosis in those regions. A ventricular aneurysm-related infarct or left ventricular dysfunction can result in the formation of left ventricular thrombi that can embolize and cause thromboembolism, including stroke[18].

1.11 Management of ACS in acute setting

1.11.1 Early treatment strategy

According to ACC/ACCF/AHA STEMI and NSTE-ACS practice guidelines, pharmacotherapy that all patients should receive within the first day of hospitalization, and preferably in the ED, are intranasal oxygen (if oxygen saturation is low), sublingual (SL) nitroglycerin (NTG), ASA, a P2Y12 inhibitor (agent and timing of administration dependent on reperfusion strategy), and anticoagulation (agent dependent on reperfusion strategy). Intravenous (IV) NTG may be given in select patients with either acute HF, severe hypertension, or who are still experiencing pain despite SL NTG. It is reasonable to administer morphine to patients with refractory angina as an analgesic and a vasodilator. Oral β-blockers should be initiated within the first day in patients without cardiogenic shock or other contraindications[8,9]. ACE inhibitors (or ARB in ACE inhibitor-intolerant patients) should be initiated in select patients during hospitalization with ACS[8]. High-intensity statin therapy should be initiated or continued during hospitalization in all patients without contraindications[8,9].

1.11.2 Reperfusion Strategies for ACS

Early reperfusion therapy with primary PCI of the infarct artery within 90 minutes from the time of first medical contact is the reperfusion treatment of choice for patients with STEMI who present within 12 hours of symptom onset[8]. Patients

may not often recognize the importance of seeking immediate medical care for a variety of reasons, which include self-treatment and preconception regarding the importance or presentation of a heart attack. Thus, education for patients and their families about the symptoms of ACS is paramount to reduce delays in reperfusion. For primary PCI in STEMI, the patient is taken from the ED to the cardiac catheterization laboratory and undergoes coronary angiography with either balloon angioplasty or, preferably, placement of a drug-eluting intracoronary stent in the artery associated with the infarct. In most cases, drug-eluting stents are preferred over bare metal stents[19,20].

Because of the high likelihood of a complete coronary artery occlusion in patients presenting with symptoms and ST-segment elevation, results of a troponin blood test do not need to be available when the decision to proceed to primary PCI is made. Findings from a meta-analysis of trials comparing fibrinolysis with primary PCI indicate a lower mortality rate with primary PCI[21]. One reason for the superiority of primary PCI compared with fibrinolysis is that more than 90% of occluded infarct-related coronary arteries are opened with primary PCI compared with fewer than 60% with fibrinolytics[8]. In addition, intracranial hemorrhage (ICH) and major bleeding risks from primary PCI are lower than the risks of severe bleeding events following fibrinolysis[22]. A strategy of primary PCI is generally preferred in patients presenting to institutions with skilled interventional cardiologists and a catheterization laboratory immediately available, those in cardiogenic shock, those with contraindications to fibrinolytics, and those with continuing symptoms 12 to 24 hours after symptom onset[8].

1.11.3 Fibrinolytics therapy for STEMI

Large clinical trials have proven that administration of a fibrinolytic agent reduces mortality Early mortality from STEMI Was reduced by approximately one-third (from 1 0%-1 5% to 6%-1 0%) with fibrinolytic therapy[23]. The fibrinolytic drugs currently used for STEM! patients in the United States are alteplase (t-PA), reteplase (r-PA), and tenecteplase (TNK). Alteplase is a naturally occurring enzyme produced by recombinant DNA technology. It cleaves the same plasminogen peptide bond that urokinase cleaves. However, t-PA has a binding site for fibrin, which allows it to bind to and preferentially lyse thrombin-bound instead of circulating plasminogen. Reteplase is a genetically modified plasminogen activator that is similar to t-PA.

Reteplase has a longer half-life, allowing it to be administered as two bolus injections 30 minutes apart, rather than as a bolus plus infusion. TNK is a genetically modified form of t-PA. Compared with t-PA, TNK has a longer plasma half-life, better fibrin specificity, and higher resistance to inhibition by plasminogen-activator inhibitor. [24,25]

1.11.4 Early Invasive Therapy for NSTE-ACS

Clinical practice guidelines recommend coronary angiography followed by either PCI or CABG surgery revascularization as an early treatment (early invasive strategy) for patients with NSTE-ACS at an elevated risk for death or MI including those with confirmed MI (by troponin or hs-troponin), a highrisk score or patients with refractory angina, hemodynamic instability, or electrical instability (eg, ventricular arrhythmias).[9,20,26] Several clinical trials support an "invasive" interventional strategy with early angiography and PCI or CABG versus an ischemia-guided approach, whereby coronary angiography with revascularization is reserved for patients with symptoms refractory to pharmacotherapy and patients with signs of ischemia on stress testing.[9,27] An early invasive approach results in a long-term reduction in the rates of CV death or MI, with the largest absolute effect seen in higher-risk patients.[9] Several studies have also shown less angina, fewer hospitalizations, and improved quality of life with an invasive strategy.[20,27]

1.11.5 Ischemia-Guided Therapy ("Medical Management") for ACS

For patients with NSTE-ACS, an initial conservative ischemic guided strategy is recommended for patients with a low-risk score, normal ECGs, and negative troponin who are without recurrence of chest discomfort.[8] An ischemia-guided strategy may also be preferred in patients with extensive comorbidities in which the cumulative risks of comorbidities plus revascularization would outweigh the potential benefits of revascularization. Stress testing is indicated in patients with NSTE-ACS when an initial ischemia-guided strategy is selected. It is also reasonable for STEMI patients who may be candidates for revascularization but did not undergo coronary angiography.[8,9] Following the stress test, patients experiencing recurrent ischemia or symptoms despite optimal medical treatment or who are considered high risk should undergo left heart catheterization with coronary angiography and revascularization as indicated.[9,23] Patients with NSTE-ACS at low risk for recurrent CHD events following stress testing should be given low-dose ASA indefinitely and either clopidogrel or ticagrelor for up to 12 months following hospital discharge in addition to other

secondary preventive pharmacotherapy described later in this chapter.[9] Patients with STEMI at low risk for recurrent CHD events should receive low-dose ASA indefinitely and clopidogrel for at least 14 days and up to 12 months in addition to other secondary preventive pharmacotherapy.[8]

1.12 Secondary Prevention Following MI

The long-term goals following ACS are to (a) control modifiable CHD risk factors; (b) prevent the development of HF; (c) prevent new or recurrent MI and stroke; (d) prevent death, including sudden cardiac death; and (e) prevent stent thrombosis following PCI. Pharmacotherapy, which has been proven to decrease mortality, HF, reinfarction, stroke, and stent thrombosis should be initiated prior to hospital discharge for secondary prevention. Secondary prevention therapies following MI include long-term treatment with ASA, and/or a P2Y12 inhibitor, β-blocker, an ACE inhibitor, and a statin for secondary prevention of death, stroke, or recurrent infarction.[9] A P2Y12 inhibitor should be continued for at least 12 months for patients undergoing PCI and for patients with NSTE-ACS receiving an ischemia-guided treatment strategy.[8,9,26]

Clopidogrel should be continued for at least 14 days and ideally up to 1 year in patients with STEMI receiving thrombolytics. Other P2Y12 inhibitors have not been studied in combination with thrombolytics; however, prasugrel may be an alternative to clopidogrel in patients who undergo delayed PCI after thrombolytics.[8] An ACE inhibitor or ARB and an aldosterone antagonist should be given to select patients. For all patients with ACS, treatment and control of modifiable risk factors such as HTN, dyslipidemia, obesity, smoking, and DM are essential.[8,9] Patients should receive proper counseling and education, both verbal and written, regarding these treatments and recommendations prior to discharge. At follow up appointments, medication reconciliation and dose optimization improve drug adherence.[28]

1.13 Study objectives

1.13.1 General objective:

To evaluate the use of secondary prevention medications of acute coronary syndrome patients'.

1.13.2 Specific objectives:

1. To recognize whether patients with ACS received dual antiplatelet, statins, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARBs), and beta-blockers at discharge from a cardiology unit.
2. To assess whether statins, ACEI/ARBs and beta-blockers were prescribed at target doses based on international guidelines.
3. To determine the correlation between demographic data and the optimal use of secondary prevention medications.
4. To detect the correlation between the comorbidities and the optimal use of secondary prevention medications.
5. To describe the effect of contraindications on the optimal use of secondary prevention medications.

Chapter two: Literature review

2. Literature review

2.1 Dual antiplatelet therapy

Antiplatelet therapy with aspirin should be lifelong for patient with ACS because of aspirin's beneficial effects on reinfarction. The ACC /AHA guidelines recommend a dose of 81 to 325 mg daily indefinitely with a preferred maintenance dose of 81 mg daily.[23,29] Dual antiplatelet therapy with clopidogrel or ticagrelor and aspirin, compared with aspirin alone, reduces major cardiovascular events in patients with established ischemic heart disease.[30,31] The use of dual antiplatelet therapy with a P2Y 12 inhibitor for patients who have undergone coronary stenting reduces the risk of future stem thrombosis.[32] In ACS patients, ideally the P2Y 12 inhibitor should be continued for at least 1 year regardless of the type of coronary stem. Data from the Dual Anti platelet Therapy (DAPT) trial found that dual antiplatelet therapy with clopidogrel or prasugrel continued for 30 months after placement of a drug-eluting stem significantly reduced the risk of stem thrombosis and major adverse cardiovascular and cerebrovascular events compared with 12 months of therapy; but was associated with an increased risk of bleeding.[32,33]

2.2 Beta blockers

The ACC I AHA guidelines recommend continued ,B-blocker therapy at discharge for all patients after ACS.[23,34] The benefits of , B-blockers in reducing reinfarction and mortality outweigh the risk, even in patients with asthma, depression, insulin-dependent diabetes, severe peripheral vascular disease, first-degree heart block, and moderate LV dysfunction. Atenolol, propranolol, carvedilol, metoprolol tartrate, and metoprolol succinate are generic, making them cost-effective. Metoprolol succinate, carvedilol, and bisoprolol are considered first-line choices in patients with HF, whereas atenolol, metoprolol tartrate, or metoprolol succinate should be considered in patients with stable asthma or bronchospastic pulmonary disease. Being discharged on a , B-blocker is a quality performance measure.[35] However, debate exists surrounding the duration of use, especially in low-risk patients without compelling indications.[23]

According to One RCT and eight observational studies, containing 47,339 patients with AMI, were included. Compared with non-use of B-blockers, B-blocker use after discharge may have reduced the risk of all-cause mortality (OR: 0.70, 95% CI: 0.61 to 0.80, I^2 = 14.4%), cardiac death (OR: 0.63, 95% CI: 0.44 to 0.91, I^2 = 22.8%),

myocardial infarction (OR: 0.73, 95% CI: 0.62 to 0.86, $I^2 = 0$), and revascularization (OR: 0.92, 95% CI: 0.85 to 0.99, $I^2 = 0$). No significant differences were found in major adverse cardiovascular events (MACE, OR: 0.88, 95% CI: 0.66 to 1.17, $I^2 = 78.4\%$), heart failure (OR: 0.56, 95% CI: 0.29 to 1.08, $I^2 = 0$) or stroke (OR: 1.13, 95% CI: 0.92 to 1.39, $I^2 = 0$). For patients with preserved left ventricular function, B-blocker use after discharge may have also reduced the risk of all-cause mortality (OR: 0.61, 95% CI: 0.44 to 0.84, $I^2 = 0$)[34].

2.3 Lipid lowering agent

A complete fasting lipid profile would be helpful and should be completed within 24 hours of presenting with an AMI.[23] This is often overlooked or not done because the patient is not fasting. Most patients will require a low-cholesterol, low-saturated fat diet in addition to lipid-lowering therapy. The ACC/AHA STEMI And NSTEMI-ACS guidelines recommend that a high-intensity statin therapy be initiated or continued in all patients with ACS unless contraindications are present.[23,36] This would consist of atorvastatin 40 to 80 mg or rosuvastatin 20 to 40 mg daily.[36] When triglycerides are 500 mg/ dL or more, drug therapy with niacin or a fibrate is beneficial.[37] The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial evaluated NSTEMI-ACS patients receiving atorvastatin 80 mg/ day or placebo within 24 to 96 hours of hospitalization. A significantly lower rate of death and nonfatal major cardiac events at 4 months of follow-up was seen in patients receiving atorvastatin.[23,38] The A to Z trial showed a favorable trend toward major cardiovascular event reduction in AMI patients receiving an intensive simvastatin regimen (40 mg/ day for 1 month followed by 80 mg/ day thereafter) when initiate within 12 hours of stabilization compared to a less intensive regimen (placebo for 4 months followed by simvastatin 20 mg/ day).[23]

Among elderly patients, the benefit of lipid lowering therapy as secondary prevention was assesses using 23 trials that enrolled 60,194 elderly patients. For secondary prevention, statins reduced all-cause mortality (RR: 0.80, 95% CI: 0.73 to 0.89), cardiovascular mortality (RR: 0.68, 95% CI: 0.58 to 0.79), CAD (RR: 0.68, 95% CI: 0.61 to 0.77), MI (RR: 0.68, 95% CI: 0.59 to 0.79), and revascularization (RR: 0.68, 95% CI: 0.61 to 0.77). Intensive (vs less-intensive) statin therapy reduced the risk of CAD and heart failure. Niacin did not reduce the risk of revascularization, and fibrates did not reduce the risk of stroke, cardiovascular mortality, or CAD.[36]

2.4 ACE Inhibitors and ARBs

ACE inhibitors reduce mortality, decrease reinfarction, and prevent the development of HF with recent ACS, especially in those with reduced LVF[8,9]. Additional trials suggest that most patients with CAD, not just ACS or HF patients, benefit from ACE inhibitors. Therefore, ACE inhibitors should be considered in all patients (eg, those with HTN, DM, or stable CKD) following an ACS in the absence of a contraindication. Besides hypotension, the most frequent adverse reaction to an ACE inhibitor is cough, which may occur in up to 30% of patients. Patients who cannot tolerate an ACE inhibitor may be prescribed an ARB. Other, less common but more serious adverse effects of ACE inhibitors and ARBs include acute renal failure, hyperkalemia, and angioedema.[8]

2.5 Mineralocorticoid Receptor Antagonist

Aldosterone plays an important role in HF and in MI because it promotes vascular and myocardial fibrosis, endothelial dysfunction, HTN, left ventricular hypertrophy, sodium retention, potassium and magnesium loss, and arrhythmias. Aldosterone antagonists have been shown to attenuate these adverse effects and reduce mortality in patients who are already receiving an ACE inhibitor (or ARB) and β-blocker and have an LVEF less than or equal to 40% (0.40) and either HF symptoms or DM.[8,9] Eplerenone and spironolactone are aldosterone antagonists that block the mineralocorticoid receptor. In contrast to spironolactone, eplerenone has no effect on the progesterone or androgen receptor, thereby minimizing the risk of gynecomastia, sexual dysfunction, and menstrual irregularities. In a large clinical trial, eplerenone significantly reduced mortality as well as hospitalization for HF in post-MI patients with an LVEF less than 40% and symptoms of HF at any time during hospitalization.[38]

The risk of hyperkalemia increases with the use of aldosterone antagonists when added to an ACE inhibitor or ARB. Therefore, patients with serum potassium concentrations greater than 5.0 mmol/L should not receive these agents. Specific contraindications for spironolactone include SCr greater than or equal to 2.5 mg/dL for men or 2.0 mg/dL for women, or CrCl less than or equal to 30 mL/min . Contraindications for eplerenone include SCr greater than or equal to 2.0 mg/dL for men or 1.8 mg/dL for women, or CrCl less than or equal to 50 mL/min. Currently, there are no data to support that eplerenone is superior or preferred to spironolactone

but it may be an option in patients who experience adverse effects including gynecomastia, breast pain, or impotence while receiving spironolactone[23].

Chapter three : Methods

3. Methods

3.1 Study design

This is multicenter retrospective descriptive cross-sectional study was conducted by reviewing patients' medical files in three hospitals (two private hospitals and one public hospital) during the study period.

3.2 Study setting and duration

This study was conducted in three hospitals, including University of Science and Technology Hospital (USTH), Al-Thawra Modern General Hospital, and Lebanon Hospital during the period from January 2020 to December 2021.

3.3 Including and excluding criteria

Patients who is 18 years or older and admitted to one of the targeted hospitals with acute coronary syndrome, including STEMI, NSTEMI, or Unstable angina during the study period were included. Patients were excluded if they discharged against medical advice, transferred to other hospital, died during hospitalization, were not diagnosed with ACS at hospital admission, or incomplete patients' medical files.

3.4 Study tool

Previously validated questionnaires were used for this study with slight modifications on their items.[7] To ensure the validity of the content, the study instrument was reviewed by a clinical pharmacist holding a master's in Clinical Pharmacy.

The data collection sheet was involved five different parts: the first section was patients' demographic data, including age, sex, habit, and marital status. The second section incorporated questions related to types of ACS, comorbidities, invasive treatment strategy (PCI), non-invasive treatment strategy (non-PCI), risk factors (eg, diabetes, hypertension, dyslipidemia, chronic renal failure, current smoker, family history of CVD, and obesity), underline disease (eg, diabetes, hypertension, heart failure), laboratory investigations (eg, serum creatinine, complete blood count, lipid profile, potassium, and ejection fraction). The third section involved assessment of vital signs at discharge, including mean systolic blood pressure, mean diastolic blood pressure, and mean heart rate. The fourth section incorporated information about patients' contraindications for certain medications, including active bleeding,

bradycardia (HR<55 BPM), hyperkalemia, acute kidney injury. The final section incorporated data related to the prescribed medications (eg, aspirin, clopidogrel, β-blocker, statin, and ACE-I /ARB) at discharge (see Appendix A).

3.5 Sample size

All patients who were diagnosed as ACS during the period from January 2020 to December 2021 and had medical files in one of the target hospitals were included in this study after applying inclusion and exclusion criteria. Total of 775 patients' medical file were founded in this period, only 669 patients' medical file were applied with inclusion and exclusion criteria and 106 patients' medical file were excluded due to one or more of the following reasons: death of the patients, incomplete patient's file, discharge against medical advice, or transfer the patients to other hospital.

3.6 Data collection

Through retrospective patients' medical files review, the following information was collected by trained clinical pharmacists using patient data collection sheet: demographic characteristics of the patients, including age, sex, habit, and marital status s index, and types of ACS, comorbidities, invasive treatment strategy (PCI), non-invasive treatment strategy (non-PCI), risk factors (eg, diabetes, hypertension, dyslipidemia, chronic renal failure, current smoker, family history of CVD, and obesity), underline disease (eg, diabetes, hypertension, heart failure), laboratory investigations (eg, serum creatinine, complete blood count, lipid profile, potassium, and ejection fraction), vital signs at discharge (eg, mean systolic blood pressure, mean diastolic blood pressure, and mean heart rate), patients' contraindications (eg, active bleeding, bradycardia (HR<55 BPM), hyperkalemia, acute kidney injury), and prescribed medications (eg, aspirin, clopidogrel, β-blocker, statin, and ACE-I /ARB) at discharge.

3.7 Ethical approval

This study was conducted by reviewing the patients' medical files. Permission letters were delivered to the three hospitals in order to access to the documented files (see Appendix [B,C,D]). Patients' anonymity and confidentiality were maintained ,so patient's informed consents were not acquired since the data were deidentified and encoded anonymously before analysis.

3.8 Statistical analysis

Continuous variables were presented as mean and standard deviation . For categorical variables, they were represented as frequency and percentage. The Kolmogorov-Smirnov was used to assess the normality of the data. The p value was > 0.05, showing normal distribution of the data. Statistical differences among groups were evaluated using Pearson's chi-squared test or Fisher's exact test. Association between appropriate secondary prevention of ACS and other variables was studied using chi-square test. in univariable logistic regression to determine the extension of association between different variables and the appropriateness of secondary prevention of ACS. Factors that had a significant effect in univariable logistic regression were subjected to multivariable binary logistic regression in order to create a model of variables that best predict the appropriateness ACS secondary prevention. Odd rations were calculated to measure the effect of each predictor on the ACS secondary prevention of the participated. All data were analyzed using IBM SPSS Statistics version 21.0 for Windows® (IBM Corp., Armonk, NY, USA). The same program was used to prepare figures. One-way Chi-square was used to compare between different variables. A p-value <0.05 was considered statistically significant.

Chapter four : Results

4. Results

A total of 775 patients' medical file were reviewed as the following: 137 patients' medical files were included from Al-Thawra Modern General Hospital, 351 patients' medical files were included from University of Science and Technology Hospital, and 287 patients' medical file were included from Lebanon Hospital. 106 patient' medical files from the total sample were excluded due to one or more of the following criteria: death of the patients (n= 24), incomplete patient's file (n= 67), discharge against medical advice (n= 14), or transfer the patients to other hospital (n= 1). Therefore, 669 patients' cases were included in the final analysis.

4.1 Participants' sociodemographic data

The participants' sociodemographic data were as the following: the majority (74.4%, n=498) of the participants were aged between 18 -64 years, and 25.6% (n=171) of the participants were ≥65 years. Regarding the gender of the participants, the majority (78.2%, n= 523) of them were male patients and the majority (93.3%, n= 624) of them were married. Most of the participants (59.9%, n= 401) admit of having one or more bad habits, such as smoking, Khat chewing, and/or Shama use as shown in **Table 1, Figure 3,4,5,6 .**

Table 1:Sociodemographic variables of the participants

Variable		Frequency	(%)
Age	18-64	498	(74.4)
	≥65	171	(25.6)
Gender	Male	523	(78.2)
	Female	146	(21.8)
Marital status	Single	45	(6.7)
	Married	624	(93.3)
Bad habit	No	268	(40.1)
	Yes	401	(59.9)
Type of bad habit	No	268	(40.1)
	Smoking	98	(14.6)
	Khat	119	(17.8)
	Shama	11	(1.6)
	Smoking plus Khat	149	(22.3)
	Smoking plus Shama	19	(2.8)
	Khat plus Shama	5	(0.7)

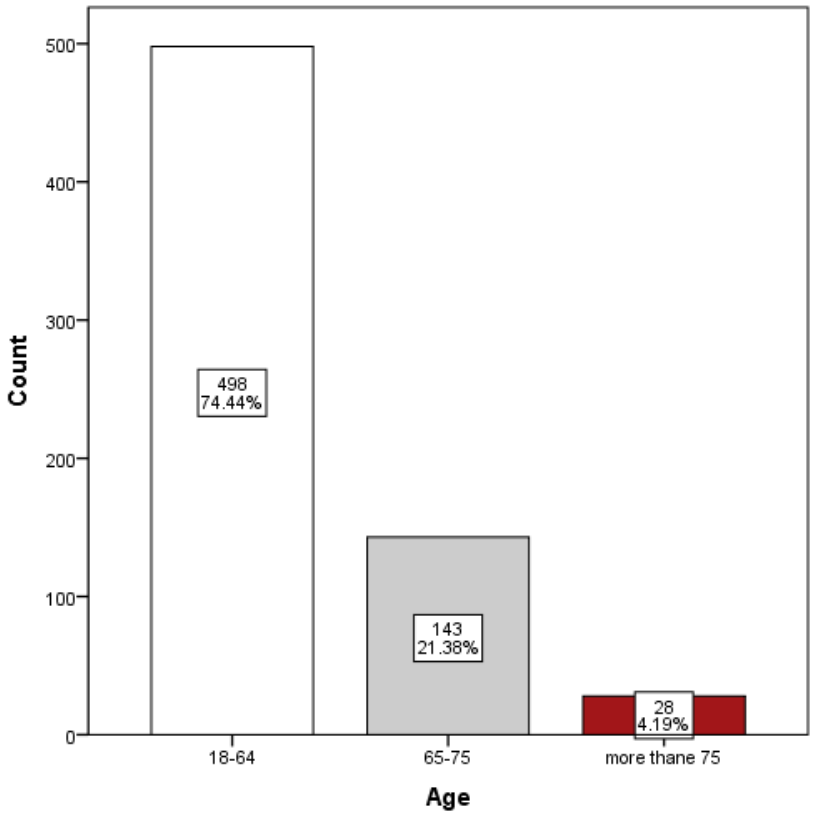

Figure 3: Participants' age

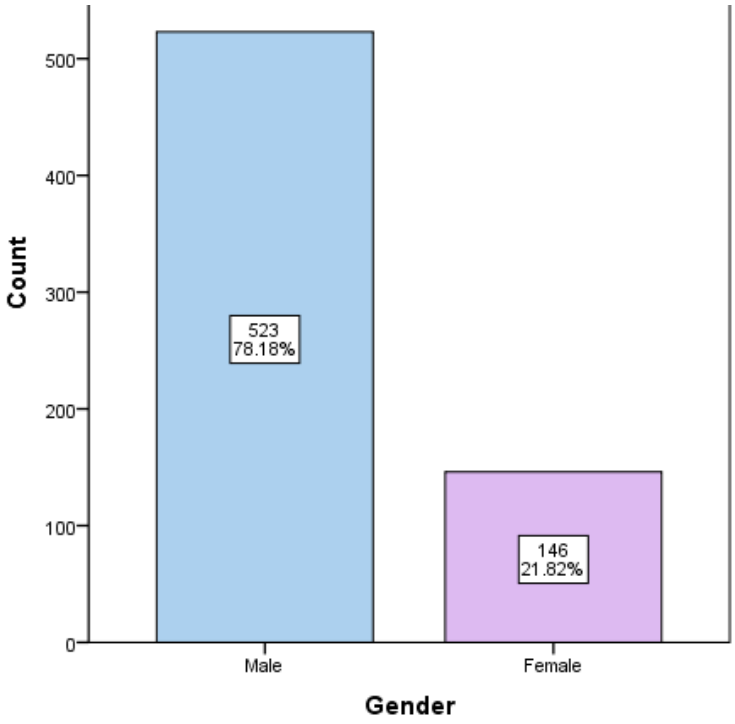

Figure 4: Gender distribution of the participants

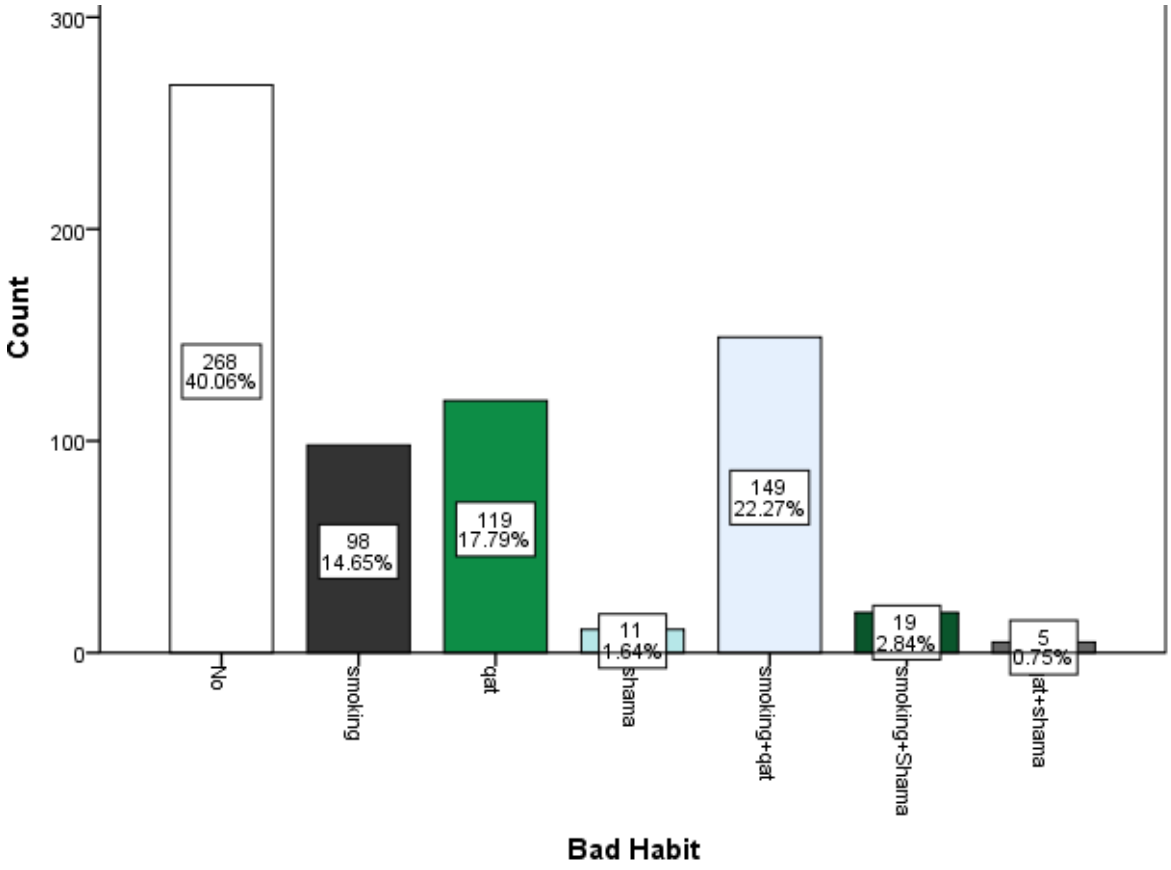

Figure 5: bad habits of the participants

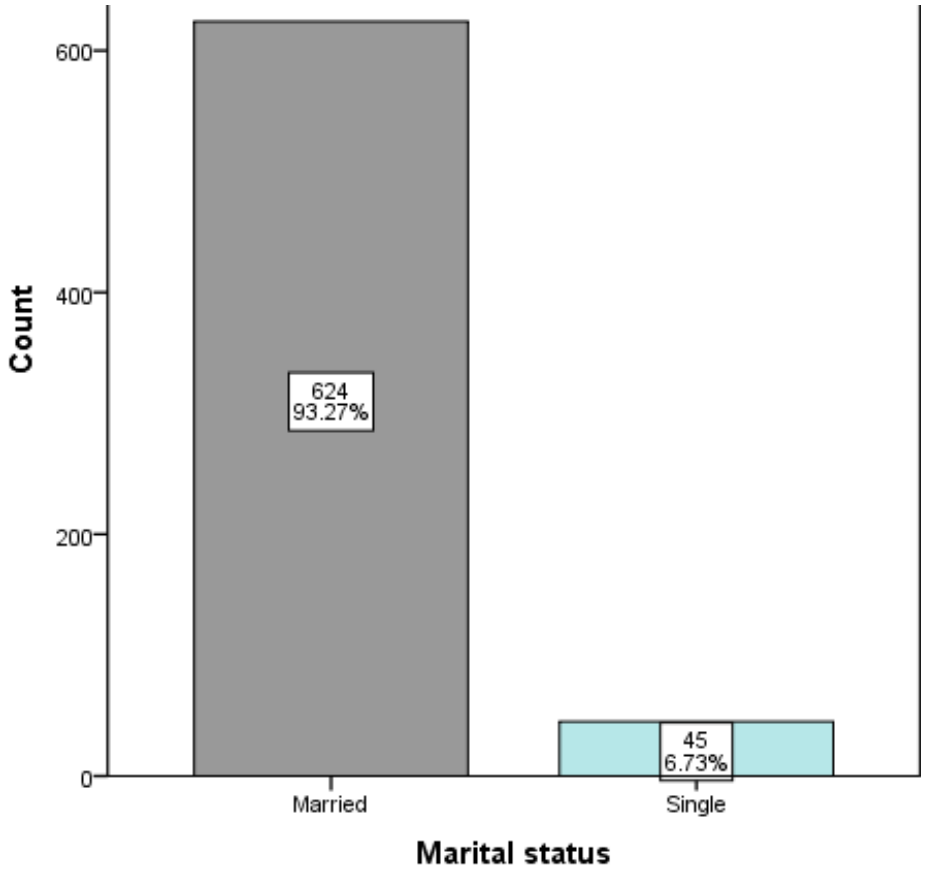

Figure 6: marital status of the participants

4.2 Participants' specific ACS, comorbidity, and type of management

The majority of the participants (65.6%, n=439) were diagnosed as STEMI followed by NSTEMI (24.5%, n=164) and UA (9.9%, n=66). Regarding comorbidity, the majority of patients showed (72.6%, n= 486) one or more comorbidity. Hypertension was the most frequently (48.3%, n=323) encountered comorbidity followed by diabetes mellitus (44.7 %, n=299). Most of patients' files (80.9%, n=541)were from private health sectors. The majority (69.1%, n= 462) of patient were treated by invasive therapy such as PCI , followed by ischemic Guided therapy (28 %, n=187), and fibrinolytic (streptokinase) therapy (3%, n=20) as shown in **Table 2, Figure 7,8,9,10.**

Table 2: diagnosis and comorbidity of the participants

Variable		Frequency	(%)
Type of ACS	STEMI	439	(65.6)
	Non-STEMI	164	(24.5)
	Unstable angina	66	(9.9)
Presence of comorbidities	No	183	(27.4)
	Yes	486	(72.6)
Number of comorbidities	No comorbidity	183	(27.4)
	One	254	(38.0)
	≥ Tow	232	(34.7)
Hypertension	No	346	(51.7)
	Yes	323	(48.3)
Diabetes Mellitus	No	370	(55.3)
	Yes	299	(44.7)
Risk factors	No risk	129	(19.3)
	Hypertension	97	(14.5)
	Diabetes	70	(10.5)
	Smoking	99	(14.8)
	Diabetes and hypertension	115	(17.2)
	Diabetes and smoking	47	(7.0)
	Hypertension and smoking	49	(7.3)
	Diabetes and hypertension and smoking	63	(9.4)
Health sector	Public sector	128	(19.1)
	Private sector	541	(80.9)
Hospital	Al-Thawra Modern General Hospital	128	(19.1)

	University of Science and Technology Hospital	293	(43.8)
	Lebanon Hospital	248	(37.1)
Type of intervention	Non-PCI (conservative)	187	(28.0)
	PCI	462	(69.1)
	Streptokinase	20	(3.0)

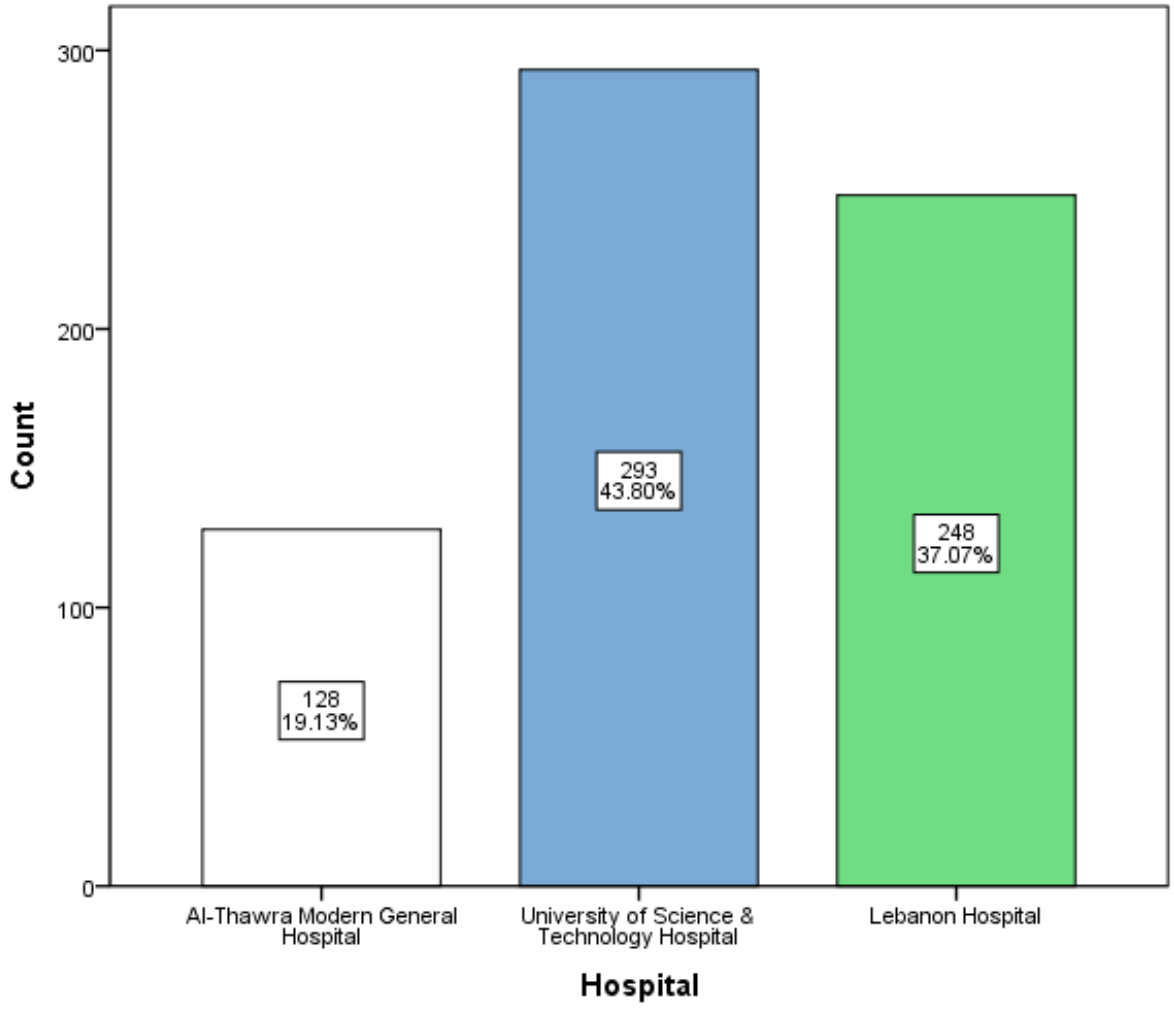

Figure 7: The study hospitals

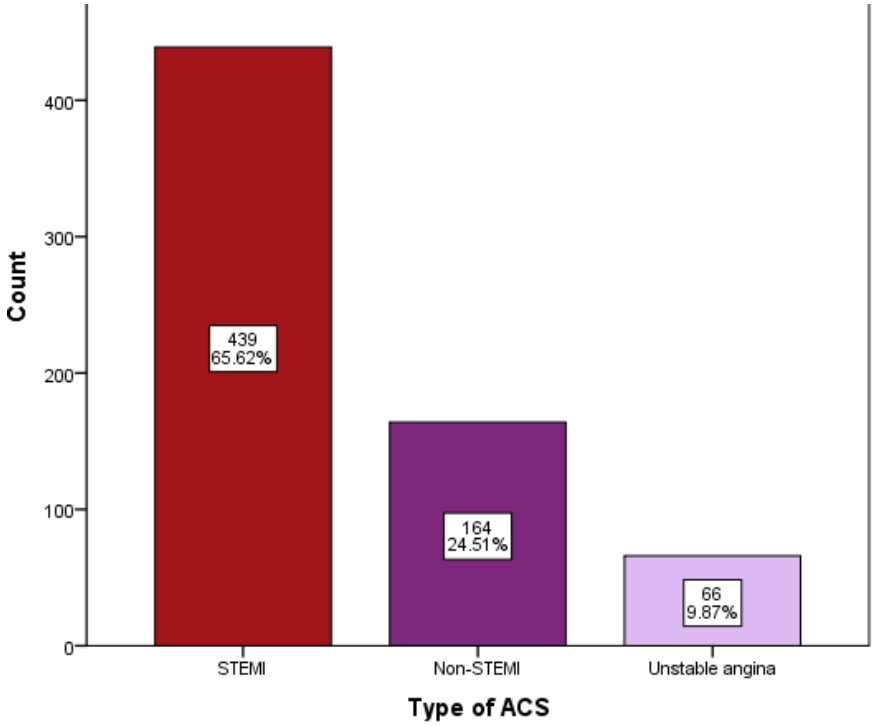

Figure 8: Diagnosis of the participants

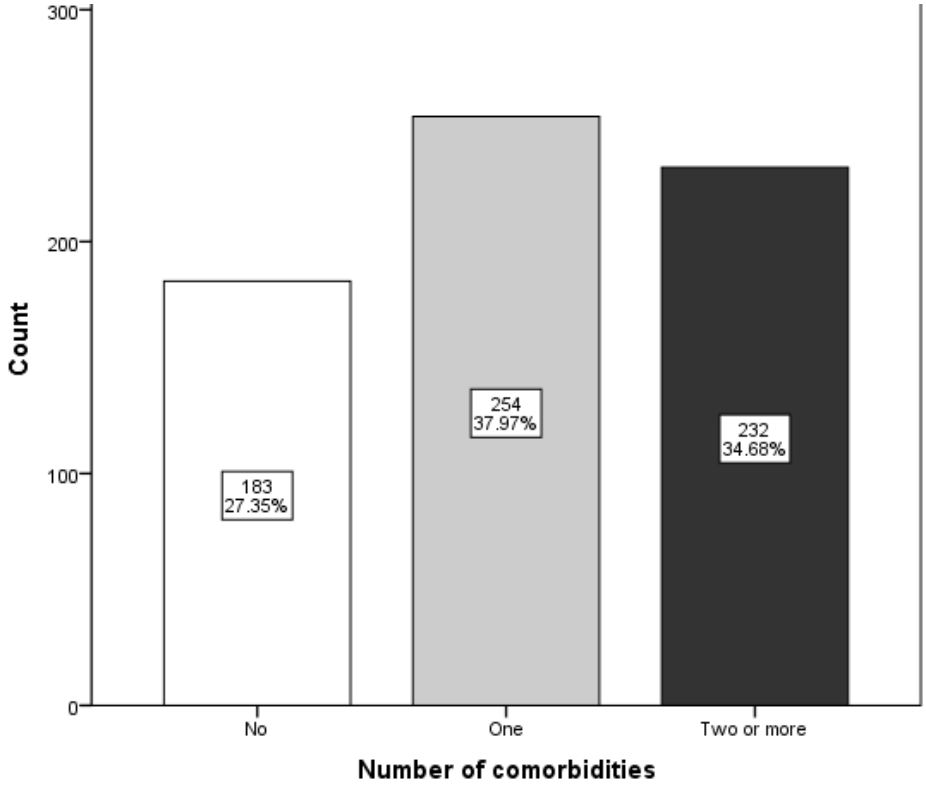

Figure 9: Participants comorbidity

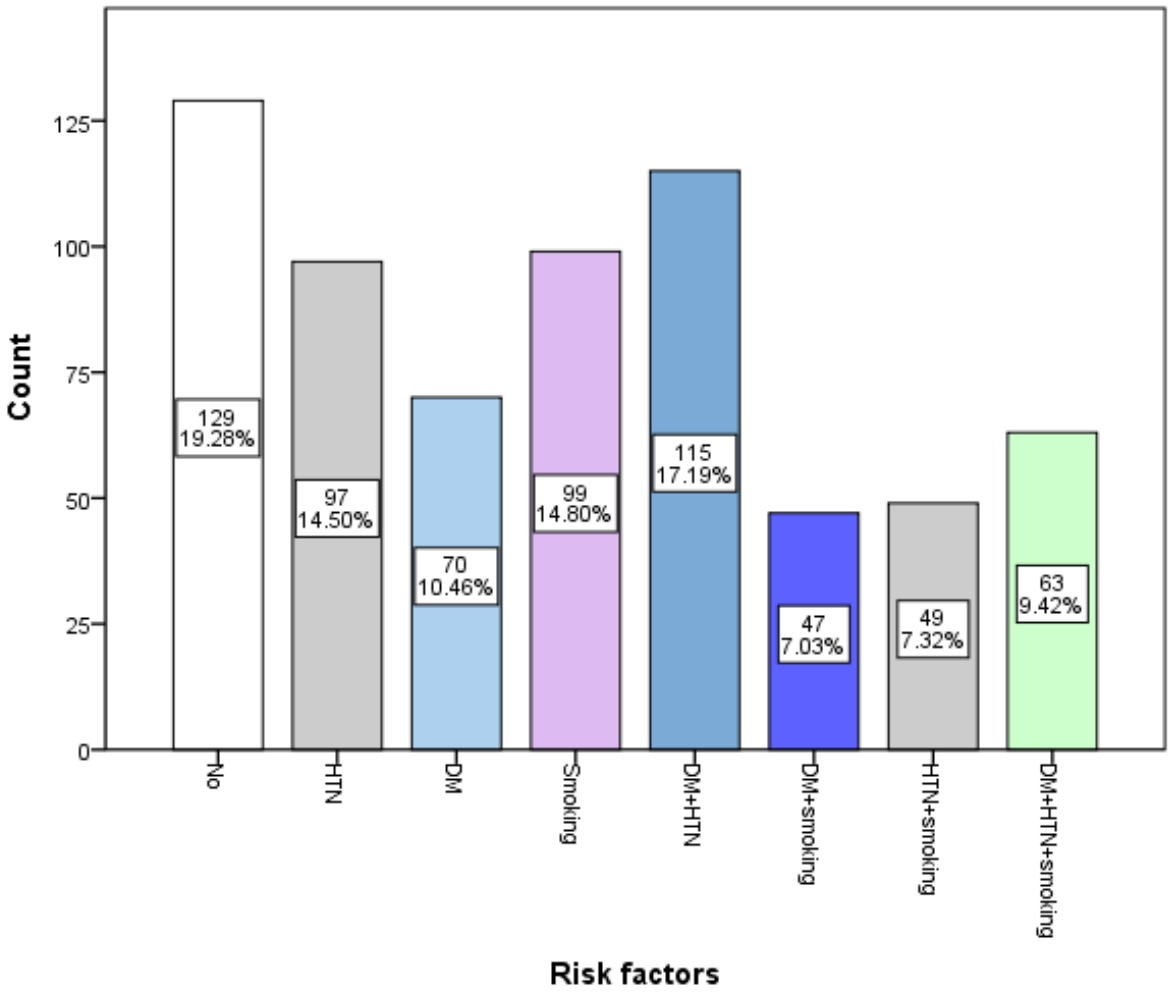

Figure 10: type of risk factors of the participants

4.3 Dispensing pattern of the five medication for ACS secondary

The majority of patients were received Aspirin (98.5%, n=659), Clopidogrel(95.1%, n=636), statin (93.3, n=624), a beta blocker (69.5%, n=465), and ACEIs/ARB (60.4%, n=404) as secondary ACS prevention. After excluding contraindications of some cases, less than half (46.5%, n=311) were received the five recommended discharge medications, including Aspirin, clopidogrel, BB, statin, and ACEI/ARB as presented in **Table 3** and **Figure 11**.

Table 3: Prescribing patterns for ACS secondary prevention

Drug		Frequency	(%)
Aspirin	No	10	(1.5)
	Yes	659	(98.5)
Clopidogrel	No	33	(4.9)
	Yes	636	(95.1)
Aspirin+ clopidogrel	No	38	(5.7)
	Yes	631	(94.3)
beta blockers drugs	No	204	(30.5)
	Yes	465	(69.5)
Statin	No	45	(6.7)
	Yes	624	(93.3)
ACEIs/ARB	No	265	(39.6)
	Yes	404	(60.4)
Discharge Medications	Aspirin + clopidogrel +BB+ statin + ACEI/ARB	302	(45.1)
	Aspirin + clopidogrel +BB+ statin	128	(19.1)
	Aspirin+ clopidogrel +statin +ACEIs/ARB	69	(10.3)
	Aspirin+ clopidogrel+ statin	100	(14.9)
	Aspirin+ statin+ BB	6	(0.9)
	Aspirin +clopidogrel +BBs	6	(0.9)
	Others	58	(8.7)
Appropriately treated using the five medications	Yes	311	46.5
	No	358	53.5

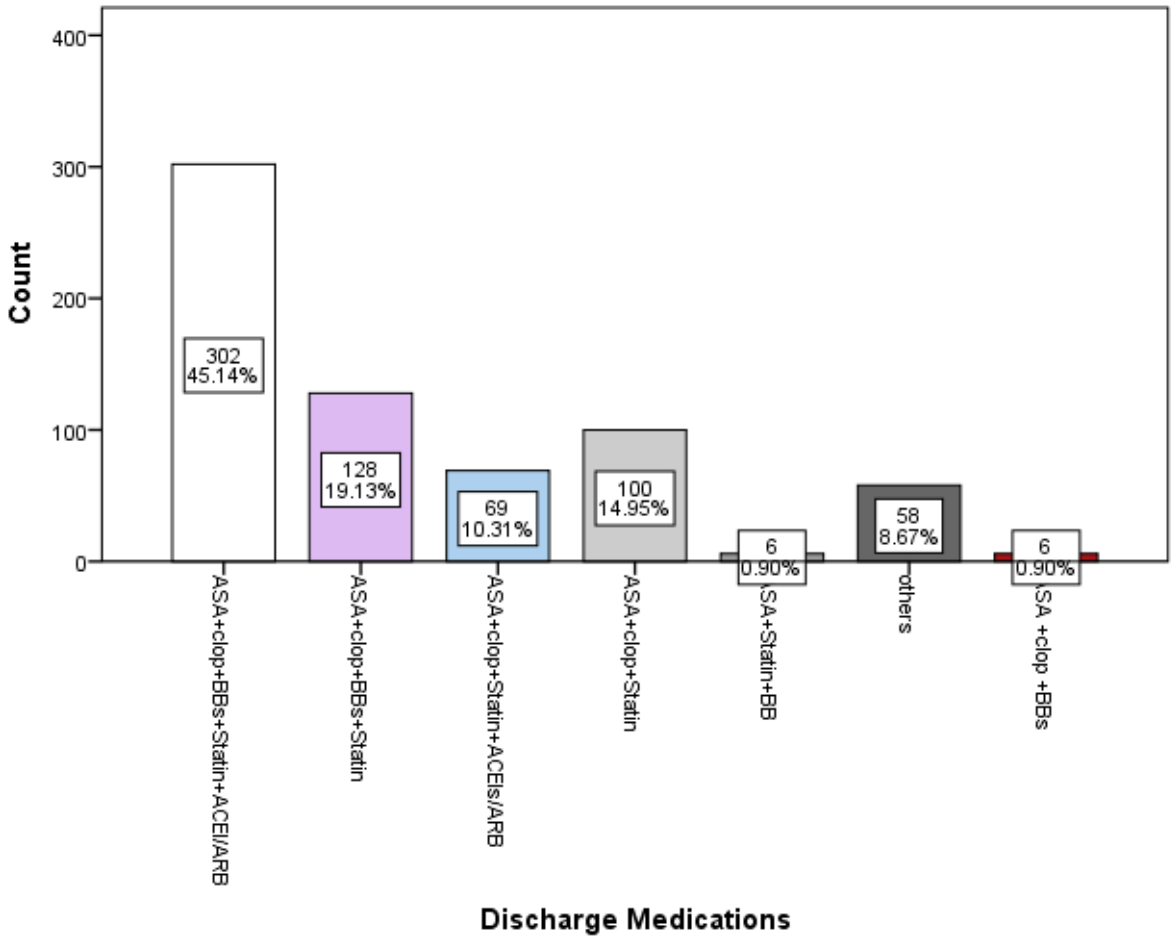

Figure 11: participants' Discharge medications

4.4 Factors that effect on the appropriateness of ACS secondary

Factors that effect on the appropriateness of ACS secondary prevention were studied. The findings of this study showed a significant association between the appropriateness of ACS secondary prevention and the type of ACS (P value = 0.006), marital status (P value =0.014), hospital (P value = 0.000), and health sector (P value = 0.000).The current study showed no significant association between the appropriateness of ACS secondary prevention and age, gender, bad habit, comorbidity, and type of risk factors as shown in **Table 4**.

Table 4: factors that effect on the appropriateness of ACS secondary prevention

Variable		Appropriateness of secondary prevention					
		Yes		No			
		Frequency	(%)	Frequency	(%)	chi-square	P- value
Type of ACS	STEMI	218	(49.7)	221	(50.3)	10.209	**0.006***
	Non-STEMI	74	(45.1)	90	(54.9)		
	Unstable angina	19	(28.8)	47	(71.2)		
Age	18-64	228	(45.8)	270	(54.2)	0.388	0.533
	≥65	83	(48.5)	88	(51.5)		
Gender	Male	239	(45.7)	284	(54.3)	0.600	0.438
	Female	72	(49.3)	74	(50.7)		
Bad habit	No	119	(44.4)	149	(55.6)	0.781	0.377
	Yes	192	(47.9)	209	(52.1)		
Marital status	Single	13	(28.9)	32	(71.1)	6.006	
	Married	298	(47.8)	326	(52.2)		**0.014***
Presence of comorbidities	No	83	(45.4)	100	(54.6)	0.130	0.719
	Yes	228	(46.9)	258	(53.1)		
Hypertension	No	161	(46.5)	185	(53.5)	0.001	0.981
	Yes	150	(46.4)	173	(53.6)		
Diabetes Mellitus	No	173	(46.8)	197	(53.2)	0.024	0.876
	Yes	138	(46.2)	161	(53.8)		
Hospital	Al-Thawra Modern General Hospital	91	(71.1)	37	(28.9)	40.370	**0.000***
	University of Science and Technology Hospital	127	(43.3)	166	(56.7)		
	Lebanon Hospital	93	(37.5)	155	(62.5)		
Health sector	Public sector	91	(71.1)	37	(28.9)	38.525	**0.000***

	Private sector	220	(40.7)	321	(59.3)		

4.5 Extent of Association Between Inappropriateness of ACS :

The extent of association between inappropriateness of ACS prevention and different variables were studies. The finding of this study showed that inappropriate ACS secondary prevention were significantly higher among patient with UA (OR = 2.44, P= 0.002), single patients (OR= 2.251, P= 0.017), and patients who were treated at private sectors (OR= 3.589, P= 0.000). on the other hand, the findings of this study did not show significant associations between inappropriate ACS secondary prevention and other variables as shown in **Table 5** .

Table 5: Variables Associated with inappropriateness of ACS secondary prevention Using Univariable Binary Logistic

Variables		Nutritional status				Univariable Binary Logistic Regression	
		Yes		No			
		N	(%)	n	(%)	OR (95% CI)	p value
Type of ACS	STEMI	218	(49.7)	221	(50.3)	Reference	
	Non-STEMI	74	(45.1)	90	(54.9)	1.200 (0.837-1.720)	0.322
	Unstable angina	19	(28.8)	47	(71.2)	2.440 (1.387-4.292)	**0.002***
Age	18-64	228	(45.8)	270	(54.2)	Reference	
	≥65	83	(48.5)	88	(51.5)	1.060 (0.789-1.582)	0.702
Gender	Male	239	(45.7)	284	(54.3)	Reference	
	Female	72	(49.3)	74	(50.7)	0.865 (0.599-1.249)	0.439
Habit	No	119	(44.4)	149	(55.6)	Reference	
	Yes	192	(47.9)	209	(52.1)	0.869(0.637-1.186)	0.377
Marital status	Married	298	(47.8)	326	(52.2)	Reference	
	Single	13	(28.9)	32	(71.1)	2.250 (1.159-4.369)	**0.017***
Presence of comorbidities	No	83	(45.4)	100	(54.6)	Reference	
	Yes	228	(46.9)	258	(53.1)	.939 (0.668-1.321)	0.719
Hypertension	No	161	(46.5)	185	(53.5)	Reference	
	yes	150	(46.4)	173	(53.6)	1.004 (0.741-1.360)	0.981
Diabetes Mellitus	No	173	(46.8)	197	(53.2)	Reference	
	Yes	138	(46.2)	161	(53.8)	1.025 (0.755-1.391)	0.876

Hospital	Al-Thawra Modern General Hospital	91	(71.1)	37	(28.9)	Reference	
	University of Science and Technology Hospital	127	(43.3)	166	(56.7)	3.125 (2.057-5.024)	**0.000***
	Lebanon Hospital	93	(37.5)	155	(62.5)	4.099 (2.585-6.497)	**0.000***
Health sector	Public sector	91	(71.1)	37	(28.9)	Reference	
	Private sector	220	(40.7)	321	(59.3)	3.589 (2.360-4.456)	**0.000***

4.6 Extent of Association Between Inappropriateness of ACS :

Five variables were included in the multivariable logistic regression model. Participants who were diagnosed as UA had OR = 2.33 (P = 0.004) of being inappropriately received ACS secondary prevention compared with patients who were diagnosed as STEMI. Participants who were single had OR= 2.107 (P value= **0.034)** of being inappropriately received ACS secondary prevention compared with married patients. Finally, Patients who were hospitalized in a private health care sector had OR=3.95 (P value= **0.000)** of being inappropriately received ACS secondary prevention compared with patients in public sectors as shown in **Table 6**.

Table 6: Variables Associated with inappropriateness secondary prevention of ACS Using Multivariate Binary Logistic regression

Variables		**Nutritional status**				**Multivariable Binary Logistic Regression**	
		Yes		**No**			
		n	**(%)**	**N**	**(%)**	**OR (95% CI)**	**p value**
Type of ACS	STEMI	218	(49.7)	221	(50.3)	Reference	
	Non-STEMI	74	(45.1)	90	(54.9)	1.195 (0.837-1.720)	0.349
	Unstable angina	19	(28.8)	47	(71.2)	2.330 (1.387-4.292)	**0.004***
Marital status	Married	298	(47.8)	326	(52.2)	Reference	
	Single	13	(28.9)	32	(71.1)	2.107 (1.059-4.191)	**0.034***
Hospital	Al-Thawra Modern General Hospital	91	(71.1)	37	(28.9)	Reference	
	University of Science and Technology Hospital	127	(43.3)	166	(56.7)	2.95 (1.870-4.656)	**0.000***
	Lebanon Hospital	93	(37.5)	155	(62.5)	3.950 (2.484-6.282)	**0.000***
Health sector	Public sector	91	(71.1)	37	(28.9)	Reference	
	Private sector	220	(40.7)	321	(59.3)	3.950 (2.484-6.282)	**0.000***

Chapter five : Discussion

5. Discussion

5.1 Main findings and significance

There is a lack of evaluating ACS secondary prevention in Yemen , as well as an increase in the number of ACS patients, which leads to increased death. This study is considered the first study to address secondary pharmacotherapy prevention to detect the gaps between the recommended and what is prescribed for ACS medications at the time of discharge.

Our study denoted that 98.5% of patients were on aspirin and 95.1% on clopidogrel; this is in line with studies conducted in Iraq, Lebanon, and Korea.[4] Yet, these percentages were higher than Ethiopian and Bangladesh studies[39,40]. Similarly, 94.3% were on dual antiplatelet aspirin plus clopidogrel, which was agreed with Bangladesh study[41].

In this study, less than half (45.1%) of patients received all five recommended medications. Which is less than the AHA / ACC guidelines, but at the same time better than a previous study conducted in Thailand that was 43.7% [42], and was lower than other studies conducted in some countries, for example 62.9% in Lebanon[43], 60% in Iraq[4] and 76% in Korea[44] were discharged on optimal five recommended secondary prevention medications. The variation between results might be due to the study time points, study designs, and the definition of optimal pharmacotherapy secondary prevention.

As compared to other cardiac medications, there was a trend towards lower prescribing rates for ACEIs and ARBs in our study (60.4%) this result consider lower than result of other study conducted by Sheikh-Taha et. al which showed prescribing rates for ACEIs and ARBs about 81.9% .[43]

In our study, 19.1 % of patients were receiving concomitantly all 4 medications, (Aspirin + clopidogrel +BB+ statin), This percentage was close to another study conducted by Danchin et al. In France, which showed 27%[45]. On the other hand, our percentage is lower than that described in other studies from different countries has reported optimal medical therapies at hospital discharge. Lee et al. reported in their study done in Korea that the discharge prescription rate of all 4 medications was 50.4% [46]. Wai et al. reported the percentage to be 57% in Australia [47]. The prescription rate was 48% in China as reported by Bi et al.[48]. This study showed a

high rate of prescribing statins (93.3%),This finding is generally similar to a study conducted in Iraq (94%) [4] and higher than study conducted in Lebanon was 89% [43]. Noteworthy from this study, about 44.7% of ACS patients had diabetes which is known as a strong risk factor for ACS , this is in agreement with a study conducted in Sudan by Byeon et al. which showed that nearly 44.5% of ACS patients had diabetes[44]. About clinical diagnosis of ACS, 49.7%, 45.1%, or 28.8% of patients in this study were diagnosed with STEMI, UA, or NSTEMI, respectively, which was consistent with the previous studies, Also, our study noted statistical differences in the use of secondary prevention therapy at discharge based on the type of ACS. STEMI ,Non-STEMI and Unstable angina were more likely to receive five-drug combination therapy . Similar findings were also observed in previous studies[49,50].

Through the results of this study. We found the types of ACS are a strong factor with the inappropriateness of ACS secondary prevention at a p-value less than 0.002 as well as marital status, hospital and health sector were found to strongly correlation with the inappropriateness of ACS secondary prevention.

5.2 Strengths and limitations of study

5.2.1 Strengths

This study has several strengths, including 1) this is the first study that assessed pharmacotherapy secondary prevention after ACS in Sana'a, which faced many challenges in the weak healthcare system, 2) The investigation is extracted from real-world data of the largest 3) the study provides data for quality and policymakers towards the improvement of documentation systems and to a step for the establishment of guidelines that suit our context. Moreover, there is a great opportunity to optimize care for patients with cardiovascular disease including ACS through the addition of a clinical pharmacist to the multidisciplinary team at Heart Center.

5.2.2 limitations

The study has some limitations. Including: The system has been broken at University of Science and Technology Hospital from 1/1 to 1/6 of 2020. The study was limited by data accuracy due to record-keeping errors, such as undocumented contraindications or medication intolerance.

Chapter six : Conclusions and Recommendations

6. Conclusion and Recommendation

6.1 Conclusion:

Approximately 45.1% of patients received the recommended secondary prevention medications at discharge from the hospital. Although this percentage was suboptimal, the results we obtained need implementation of strategies to optimize prescribing. Certain factors, such as having UA, marital status , and health sector may have effect on the appropriate ACS secondary prevention.

6.2 Recommendation:

Through our study we recommend the following:

1. We recommend repeating this study with prospective design, to control confounding factors and biases of retrospective.
2. Conduct more studies regarding the outcomes, such as changes in laboratory parameters of ACS patients according to the prescription patterns of discharge medications for ACS in the near future.
3. Involvement of clinical pharmacists within the cardiology multidisciplinary team is necessary, to facilitate adherence to guidelines and empower the importance of medication adherence

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Appendices

Appendix A : Data collection sheet

File number :_____ Age: 18-64 ( ) ,65-75 ( ) ,more ( )

Gender : male / female Habit : smoking ,qat , shama

Martial status : single , married , widow

Diagnosis						
	✓ ✗		✓ ✗		✓ ✗	Note
STEM		NSTEM		Unstable angina		
Past medical history						
HTN		DM		HF		
Comorbidities :_____						
PCI		Non PCI				
Risk factors						
HTN		DM		Obesity		
Smoker		Family history CVD		CKD		
Paste medication history _____						

Laboratory test								
Scr		Platelet		K		EF		
Lipid profile								
Vitals at discharge								
SBP		DBP		HR				

Drugs	yes	no	Dose
Aspirin			
Clopidogrel			
BBs			
statin			
ACEI \ ARB			
Other			

Group	yes	no
Aspirin+ Clopidogrel		
Aspirin+ Clopidogrel+ statin		
Aspirin+ Clopidogrel+ statin+BBs		
Aspirin+ Clopidogrel+ statin+BBs +ACEI\ARB		
Aspirin+ statin+BBs +ACEI\ARB		

contraindication for using cardiac medication

Condition	Contraindication drugs	Yes	no
Active bleeding	Antiplatelet		
Bradycardia (HR 55)	BBs		
Hyperkalemia	ACEI \ ARB		
Acute renal injury	ACEI \ ARB		

Medications	Guideline adherence	Target dosing low	Target dosing medium	Target dosing high
Aspirin				
Clopidogrel				
BBs				
statin				
ACEI \ ARB				
Aspirin +Clopidogrel				
All five medication				

Medications	Target Does	Low target dosing 50%	Medium target dosing 50 -74%	High target dosing
Metoprolol	200mg			
Atenolol	100mg			
Carvedilol	50mg			
Bisoprolol	10mg			
Lisnopril	10mg			
Ramipril	10mg			
Valsartan	320mg			
Losartan	150mg			
Candesartan	32mg			
Atrorvastarin	80mg			
Rosuvastatin	20-40mg			

Appendix B : Permission letters of Al-Thawra Hospital

Republic of Yemen
Emirates International University
College of Medicine &Health Sciences
Section: pharm- D

الجمهورية اليمنية
الجامعة الإماراتية الدولية
كلية الطب والعلوم الصحية
القسم: دكتور صيدلي

الاخ/ رئيس هيئة مستشفى الثورة المحترم

تحية طيبة وبعد

الموضوع :التنسيق لطلاب قسم الصيدلة السريرية pharm-D المستوى السادس

بالاشارة الى الموضوع اعلاه نرجوا منكم التكرم بالتوجيه والسماح لطلاب الصيدلة السريرية Pharm-D المستوى السادس بتجميع المادة العلمية في ارشيف قسم الباطنة(قسم القلب) لغرض عمل بحث التخرج بعنوان:

Estimation of Drug Related Problem in Discharge Medication among Cardiac Patients in sana'a city

وعليـــــه : نرجو منكم شاكرين التكرم بالسماح للطلاب بتجميع المادة العلمية الخاصة بالبحث .

ولاتتحمل الجامعة أي مسؤولية تجاه الغير.

وتقبلوا خالص الشكروالتقدير ...

القائم بأعمال عميد شؤون الطلاب
أ.مروان الرواعي

الجمهورية اليمنية
هيئة مستشفى الثورة العام – صنعاء
الشؤون الاكاديمية والتدريب
قسم البحوث والنشر

الشؤون الأكاديمية والتدريب

الاخ / مدير أدارة الاحصاء والسجل الطبي المحترم

تحية طيبة وبعد ،،،

مرفق اليكم صورة المذكرة الواردة من الجامعة الامارتية الدولية كلية الطب والعلوم الصحية شعبة الصيدلية السريرية يرجى التعاون مع الطلاب في تسهيل تنفيذ التكليف البحثي بعنوان:

(Estimation of drug Related Problem in discharge Medication among cardiac Patients in Sana'a city

وذلك لمدة شهر واحد ابتداءً من تاريخ ٥ /٦/ ٢٠٢٢م

وتقبلوا خالص التقدير،،،

نائب المدير

د/ عبد

رئيس قسم البحوث والنشر

د/عبد

د/ عبدالله محمد حسن الشعاري
نائب رئيس الهيئة لشؤون الأكاديمية والتدريب

الشؤون الأكاديمية والتدريب

الدكتور مرفق الطلب
للسماح للمذكورين أخذ
أرحام ملفات المرضى من السجل الطبي
5

Appendix C: Permission letters of University of Science and Technology Hospital

Republic of Yemen
Emirates International University
College of Medicine &Health Sciences
Section: pharm- D

الجمهورية اليمنية
الجامعة الإماراتية الدولية
كلية الطب والعلوم الصحية
القسم: دكتور صيدلي

المحترم

الاخ مدير مستشفى جامعة العلوم والتكنولوجيا

تحية طيبة وبعد

الموضوع :التنسيق لطلاب قسم الصيدلة السريرية pharm-D المستوى السادس

بالاشارة الى الموضوع اعلاه نرجوا منكم التكرم بالتوجيه والسماح لطلاب الصيدلة السريرية Pharm-D المستوى السادس بتجميع المادة العلمية في ارشيف قسم الباطنة(قسم القلب) لغرض عمل بحث التخرج بعنوان:

Evaluation of Discharge Prescription for Secondary Prevention in Patient with Acute Coronary Syndrome

وعليـــــــه : نرجو منكم شاكرين التكرم بالسماح للطلاب التالية اسماوهم بتجميع المادة العلمية الخاصة بالبحث وهم:

1- صلاح الدين منصور
2- عماد الهادي
3- محمج البرحي
4- علي المطار
5- محسن الاسد
6- ابراهيم القرم
7- علاء الحبابي
8- هيفاء الحاضري
9- جيهان الصبري
10- منيا راشد .

ولاتتحمل الجامعة أي مسؤولية تجاه الغير.

وتقبلوا خالص الشكروالتقدير ...

القائم بأعمال عميد شؤون الطلاب
أ/ مروان الذراعي

مستشفى جامعة العلوم والتكنولوجيا

إدارة الموارد البشرية – قسم التدريب

مستشفى جامعة العلوم والتكنولوجيا
University of Science & Technology Hospital

التاريخ :١٤/٦/٢٠٢٢

نموذج موافقة جمع بيانات بحث علمي

اسم الباحث: أسماء محمد ناصر الحامد **التخصص:** صيدلة سريرية **الجامعة :** الأهلية الدولية

عنوان البحث

Evaluation of discharge prescriptions for secondary prevention in patients with acute coronary syndrome

موافقة الإدارة والقسم المعني بجمع البيانات:

القسم: الصيدلية الإدارة:

تم الاطلاع على عنوان البحث وأداة جمع البيانات ونوافق على جمع البيانات

رئيس القسم	مدير الإدارة
الاسم: د. محمد كباس	الاسم:
التوقيع:	التوقيع:

موافقة إدارة الجودة

تم الاطلاع على عنوان البحث وأداة جمع البيانات ونوافق على جمع البيانات

الاسم

التوقيع

اعتماد المدير العام أو المدير الطبي

Appendix D: Permission letter of Lebanon Hospital

Republic of Yemen
Emirates International University
College of Medicine &Health Sciences
Section: pharm- D

الجمهورية اليمنية
الجامعة الإماراتية الدولية
كلية الطب والعلوم الصحية
القسم: دكتور صيدلي

الاخ مدير مستشفى لبنان المحترم

تحية طيبة وبعد

الموضوع :التنسيق لطلاب قسم الصيدلة السريرية pharm-D المستوى السادس

بالاشارة الى الموضوع اعلاه نرجوا منكم التكرم بالتوجيه والسماح لطلاب الصيدلة السريرية Pharm-D المستوى السادس بتجميع المادة العلمية في ارشيف قسم الباطنة(قسم القلب) لغرض عمل بحث التخرج بعنوان:

Evaluation of Discharge Prescription for Secondary Prevention in Patient with Acute Coronary Syndrome

وعليـــــه : نرجو منكم شاكرين التكرم بالسماح للطلاب التالية اسماؤهم بتجميع المادة العلمية الخاصة بالبحث وهم:

1- صلاح الدين منصور
2- عماد الهادي
3- مجمع البرهي
4- علي المطار
5- محسن الاسد
6- ابراهيم القرم
7- علاء الحبابي
8- هيفاء الحاضري
9- جيهان الصبري
10- منيا راشد .

ولاتتحمل الجامعة اي مسؤولية تجاه الغير.

وتقبلوا خالص الشكروالتقدير ...

القائم بأعمال عميد شؤون الطلاب
أ/ مروان الزراعي