THE PATTERNS OF PRESCRIBING, HEALTH BELIEFS AND ADHERENCE TO STATIN THERAPY AMONG PATIENTS WITH HIGH CARDIOVASCULAR DISEASE RISK AND HEALTH CARE PROVIDERS' KNOWLEDGE, ATTITUDE, BARRIERS AND PRACTICE REGARDING CARDIOVASCULAR RISK ASSESSMENT AND STATIN THERAPY IN YEMEN

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by

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ACC	American College Of Cardiology
ACS	Acute Coronary Syndrome
ADA	American Diabetes Association
ADRS	Adverse Drug Reactions
AHA	American Heart Association
ALT	Alanine Aminotransferase
AOR	Adjusted Odds Ratios
ASCVD	Atherosclerotic Cardiovascular Disease
AST	Aspartate Transaminase
AUC	The Area Under The Curve
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
CCBs	Calcium Channel Blockers
CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
CME	Continuing Medical Education
CPD	Continuing Professional Development
CPGs	Clinical Practice Guidelines
CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
CV	Cardiovascular
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease

CYP 450	Cytochrome P450
DDI	Drug-Drug Interaction
DM	Diabetes Mellitus
DRPs	Drug-Related Problems
EAS	European Atherosclerosis Society
ED	Erectile Dysfunction
EFA	Exploratory Factor Analysis
EMR	Eastern Mediterranean Region
ESC	European Society Of Cardiology
FDA	The Food And Drug Administration
FPG	Fasting Plasma Glucose
GPs	General Practitioners
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HMG-CoA	Hydroxy-3-Methylglutaryl-Coenzyme A
HMGCR	Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase
HTN	Hypertension
ICU	Intensive Care Unit
I-CVI	Item Content Validity Index
I-CVI/Ave	Item-Content Validity Index Based On The Average Method
IDF	International Diabetes Foundation
IHD	Ischemic Heart Diseases
INR	International Normalized Ratio
IPF	International Pharmaceutical Federation
IQR	Interquartile Range
KDIGO	Kidney Disease Improving Global Outcomes Guidelines

KMO	Kaiser–Mayer–Olkin
LDL-C	Low-Density Lipoprotein Cholesterol
LMICs	Low- And Middle-Income Countries
MDR1	Multidrug Resistance-1
MENA	Middle East And North Africa
MMAS-8	8-Item Morisky Medication Adherence Scale
NCDs	Non-Communicable Diseases
NICE	National Institute For Health And Clinical Excellence
OATP1B1	Organic Anion-Transporting Polyprotein
OR	Odds Ratios
OTC	Over-The-Counter
PAD	Peripheral Artery Disease
PD	Pharmacodynamic
P-gp	Permeability Glycoproteins
PK	Pharmacokinetic
QOE	Quality Of Evidence
RCTs	Randomized Controlled Trials
ROC	Receiver-Operating Characteristics
SAMS	Statin-Associated Muscle Symptoms
S-CVI	Scale-Content Validity Index
S-CVI/UA	Scale-Content Validity Index Based On The Universal Agreement
SD	Standard Deviation
SDIs	Statin-Drug Interaction
SOR	The Strength Of Recommendation
TG	Triglycerides
TIA	Transient Ischemic Attack

UK	United Kingdom
ULN	Upper Limit Normal
USA	United States Of America
USM	Universiti Sains Malaysia
VIF	The Variance Inflation Factor
vs.	Versus
WHO	World Health Organization

LIST OF APPENDICES

CORAK PRESKRIPSI, KEPERCAYAAN KESIHATAN DAN PEMATUHAN TERAPI STATIN DALAM KALANGAN PESAKIT DENGAN RISIKO PENYAKIT KARDIOVASKULAR YANG TINGGI SERTA PENGETAHUAN, SIKAP, HALANGAN DAN AMALAN PENYEDIA PERUBATAN BERKENAAN PENILAIAN RISIKO KARDIOVASKULAR DAN TERAPI STATIN DI YAMAN

ABSTRAK

Statin digunakan secara meluas dalam amalan klinikal untuk pencegahan primer dan sekunder penyakit kardiovaskular. Pengetahuan penyedia penjagaan kesihatan tentang cadangan garis panduan terkini adalah penting untuk amalan penggunaan statin yang bersesuaian. Selain itu, kepatuhan pesakit adalah faktor utama dalam mencapai faedah yang diingini daripada terapi statin. Oleh itu, kajian ini bertujuan untuk menilai kadar, corak, dan kesesuaian preskripsi terapi statin dalam kalangan pesakit yang mempunyai indikasi klinikal. Selain itu, kajian ini bertujuan untuk menilai perkaitan antara faktor Model Kepercayaan Kesihatan (HBM) dan pematuhan kepada statin. Ia juga bertujuan untuk menilai pengetahuan, sikap, halangan dan amalan doktor dan pegawai farmasi berkenaan cadangan garis panduan terkini untuk penilaian risiko penyakit kardiovaskular aterosklerotik (ASCVD) dan terapi statin. Tambahan lagi, ia menilai kesan campur tangan pendidikan dalam meningkatkan pengetahuan dan amalan doktor dan pegawai farmasi. Kajian keratan rentas berbilang dengan intervensi pendidikan telah digunakan dalam projek ini. Lebih kurang 1200 pesakit dengan tanda-tanda klinikal untuk statin telah ditemu bual di empat hospital penjagaan tertiari di Sana'a, Yaman. Kekurangaan penggunaan dan

kesesuaian preskripsi statin telah dinilai. Pangkalan data Interaksi Ubat Lexicomp digunakan untuk menganalisis preskripsi bagi interaksi ubat statin yang berkemungkinan. Skala penarafan pematuhan ubat (MARS-10) telah diadaptasi dan disahkan untuk mengukur pematuhan terapi statin. Soal selidik HBM telah dibina dan disahkan untuk mengkaji peramal pematuhan. Selain itu, dua soal selidik telah dibina dan disahkan untuk menilai pengetahuan, sikap dan amalan 256 doktor dan 456 pegawai farmasi mengenai penilaian risiko ASCVD. Tambahan pula, satu lagi soal selidik telah dibina dan disahkan untuk menilai pengetahuan klinikal terapi statin dalam kalangan 496 penyedia penjagaan kesihatan (petunjuk klinikal, intensiti dos, interaksi ubat-ubat, kontraindikasi, dan parameter pemantauan). Akhir sekali, intervensi pendidikan telah dijalankan di hospital universiti sains dan teknologi. Ia direka bentuk untuk menilai keberkesanan intervensi dalam meningkatkan pengetahuan pakar perubatan dan ahli farmasi. Daripada 1200 pesakit dengan petunjuk klinikal untuk statin, hanya 634 (52.8%) kes menggunakan statin. Kadar penggunaan adalah lebih tinggi dalam kalangan pesakit dengan pencegahan sekunder (Nisbah Ganjil Terlaras (AOR)= 3.098, $p<0.001$), yang mempunyai bilangan komorbiditi yang lebih tinggi (AOR= 1.972, $p<0.001$), dan pesakit yang berpendapatan agak tinggi (AOR= 1.976, $p=0.001$). Daripada 634 pengguna statin, hanya 18% pesakit mempunyai corak yang sesuai untuk terapi statin. Majoriti pesakit mempunyai intensiti dos suboptimum (78.2%), 0.32% memerlukan pelarasan dos buah pinggang, dan 18% pesakit mempunyai interaksi ubat statin (SDI) yang signifikan secara klinikal. Daripada SDI ini, 102 (83.6%) adalah kelas C (pemantauan terapi), 19 (15.6%) adalah kelas D (pengubahsuaian terapi), dan hanya satu (0.8%) kelas X (elakkan kombinasi). Penggunaan simvastatin berkaitan secara signifikan dengan kehadiran kategori D dan X SDI (15.9% vs. 1.6%, $p < 0.001$). Polifarmasi (AOR= 2.571, $p <0.001$) dan mempunyai ≥3 komorbiditi (AOR= 2.512, *p* <0.001) adalah satu-satunya pemboleh ubah yang dikaitkan dengan kehadiran SDI (C, D, dan/atau X). Antara pesakit yang mempunyai bacaan LDL-C (215) terkini, hanya 65 (30.2%) adalah terkawal. Separuh daripada peserta (49.5%) mempunyai kepatuhan yang tinggi terhadap statin. Pesakit yang berumur >50 tahun (AOR= 1.777, 95% CI:1.110-2.843), mempunyai pendapatan bulanan >200$ (AOR= 2.915, 95% CI: 1.423-5.973), mempunyai insurans (AOR = 2.537, 95% CI: 1.385-4.648), mengambil statin untuk pencegahan sekunder (AOR= 2.681, 95% CI: 1.684-4.268), dengan kerentanan persepsi yang tinggi (AOR= 2.023, CI: 1.357-3.014), efikasi kendiri yang tinggi (AOR= 1.974, 95% CI:1.324-2.944), petunjuk kepada tindakan yang tinggi (AOR= 2.545, 95% CI: 1.745-3.713) lebih berkemungkinan untuk mematuhi terapi statin. Manakala, pesakit yang merokok (AOR= 0.492, 95% CI: 0.271-0.893), individu yang menggunakan statin selama lebih daripada 3 tahun (AOR= 0.479, 95% CI: 0.285-0.805), dan mereka yang mempunyai halangan persepsi yang tinggi (AOR=0.357, 95% CI: 0.241-0.530) kurang berkemungkinan untuk mematuhi terapi statin. Pakar perubatan dan pegawai farmasi menunjukkan tahap pengetahuan yang rendah dan sikap positif yang terhadap penilaian risiko kardiovaskular. Walau bagaimanapun, amalan mengenai penilaian risiko CVD dan kaunseling sebelum memulakan terapi statin adalah tidak mencukupi. Selain itu, mereka mempunyai tahap pengetahuan klinikal yang rendah mengenai terapi statin, intensiti dos, interaksi ubat-ubatan, kontraindikasi, dan parameter pemantauan. Jurang dalam pengetahuan dan amalan ini dapat dilihat dalam keadaan klinikal sebenar melalui penggunaan statin yang rendah dalam kalangan pesakit dengan indikasi klinikal. Intervensi pendidikan meningkatkan pengetahuan peserta tentang penilaian risiko ASCVD dan terapi statin. Oleh itu, kuliah pengajaran lanjutan dan program latihan melalui pendidikan perubatan berterusan mengenai garis panduan terkini perlu dilaksanakan secara berkala untuk meningkatkan kesedaran dan menambah baik kesesuaian preskripsi terapi statin. Untuk memastikan keselamatan pesakit, penyedia penjagaan kesihatan haruslah mengetahui sifat unik setiap statin, serta faktor risiko pesakit untuk interaksi ubat statin yang ketara. Pemeriksaan preskripsi secara berkala juga adalah perlu untuk meningkatkan hasil pesakit dan mengurangkan kelaziman interaksi ini. Selain itu, kepercayaan kesihatan pesakit adalah faktor penting dalam pematuhan statin dan harus ditangani dalam program intervensi berpusatkan pesakit yang disasarkan untuk menambah baik kepatuhan ubat.

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ABSTRACT

Statins are extensively used in clinical practice for the primary and secondary prevention of cardiovascular diseases (CVD). Healthcare providers' knowledge of the up-to-date guideline recommendations is essential for the appropriate utilization of statins in practice. Also, patients' adherence is a fundamental factor in achieving the desired benefits of statin therapy. Therefore, this study aimed to assess the rate, patterns, and appropriateness of statin therapy prescription among patients with clinical indications. Moreover, this study aimed to evaluate the association between the health belief model (HBM) factors and adherence to statins. Furthermore, it is meant to assess the physicians' and pharmacists' knowledge, attitude, barriers, and practices regarding the up-to-date guideline recommendations for atherosclerotic cardiovascular diseases (ASCVD) risk assessment and statin therapy. Additionally, it assessed the impact of educational intervention on improving the physicians' and pharmacists' knowledge and practices. Multiple cross-sectional studies with an educational intervention were used in this project. About 1200 patients with clinical indications for statins were recruited at four tertiary care hospitals in Sana'a, Yemen. The underutilization and appropriateness of statins prescription were assessed. The

Lexicomp Drug Interaction database was used to analyze the prescriptions for potential statin-drug interactions. The medication adherence rating scale (MARS-10) was adapted and validated to measure statin therapy adherence. HBM questionnaire was constructed and validated to investigate the predictors of adherence. Moreover, two questionnaires were constructed and validated to evaluate the knowledge, attitude, and practices of 256 physicians and 456 pharmacists regarding ASCVD risk assessment. Furthermore, another questionnaire was constructed and validated to evaluate the clinical knowledge of statin therapy among 496 healthcare providers (clinical indications, dose intensity, drug-drug interactions, contraindications, and monitoring parameters). Finally, an educational intervention was done at the university of science and technology hospital. It was designed to assess the effectiveness of the intervention in improving the knowledge of physicians and pharmacists. Of 1200 patients with clinical indications for statins, only 634 (52.8%) cases had statins. The utilization rate was significantly higher among patients with secondary prevention (adjusted odds ratio (AOR)= 3.098, $p<0.001$), who had a higher number of comorbidities (AOR= 1.972, $p<0.001$), and patients with relatively high income (AOR= 1.976, $p=0.001$). Out of the 634 statin users, only 18% of patients had an appropriate pattern for statin therapy. Most patients had suboptimal dose intensity (78.2%), 0.32% needed renal dose adjustments, and 18% had a clinically significant statin-drug interaction (SDI). Of these SDIs, 102 (83.6%) were class C (monitor therapy), 19 (15.6%) were class D (therapy modification), and only one (0.8%) class X (avoid combination). Simvastatin use was significantly associated with the presence of category D and X SDIs (15.9% vs. 1.6%, $p < 0.001$). Polypharmacy (AOR= 2.571, $p < 0.001$) and having ≥3 comorbidities (AOR= 2.512, $p < 0.001$) were the only variables associated with the presence of SDIs (C, D, and/or X). Among patients who had recent LDL-C (215), only

65 (30.2%) were controlled. Half of the participants (49.5%) were highly adherent to statins. Patients who were >50 years old (AOR= 1.777, 95% CI:1.110-2.843), had a monthly income >200$ (AOR= 2.915, 95% CI: 1.423-5.973), insured (AOR= 2.537, 95% CI:1.385-4.648), taking statins for secondary prevention (AOR= 2.681, 95% CI: 1.684-4.268), with high perceived susceptibility (AOR= 2.023, 95% CI: 1.357-3.014), high self-efficacy (AOR= 1.974, 95% CI:1.324-2.944), high cues to action (AOR= 2.545, 95% CI: 1.745-3.713) were more likely to be adherent to statin therapy. Whereas smoker patients (AOR= 0.492, 95% CI: 0.271-0.893), individuals on statins for more than three years (AOR= 0.479, 95% CI: 0.285-0.805), and those with high perceived barriers (AOR=0.357, 95% CI: 0.241-0.530) were less likely to be adherent to statin therapy. Physicians and pharmacists exhibited a low level of knowledge and a positive attitude toward cardiovascular risk assessment. However, the practices regarding CVD risk assessment and the counseling before statin therapy initiation were inadequate. Moreover, they had a low level of clinical knowledge regarding statin therapy, dose intensities, drug-drug interaction, contraindications, and monitoring parameters. These gaps in knowledge and practices were reflected in real clinical settings by the low underutilization of statins among patients with clinical indications. The educational intervention improved participants' knowledge of ASCVD risk assessment and statin therapy. Therefore, further education lectures and training programs through continuing medical education on the up-to-date guidelines should be regularly implemented to raise awareness and improve the appropriateness of statin therapy prescription. To ensure patient safety, health care providers must be aware of the unique properties of each statin, as well as patient risk factors for significant statin-drug interactions. Also, regular screening of prescriptions is necessary to improve patient outcomes and reduce the prevalence of these interactions. Moreover, patient

health beliefs are important factors in statin adherence and should be addressed in a patient-centered intervention program to improve medication adherence.

CHAPTER 1

INTRODUCTION

1.1 Cardiovascular Disease Epidemiology and Risk Factors

1.1.1 Global Epidemiology of Cardiovascular Disease

Cardiovascular disease (CVD) is a highly prevalent condition, a major contributor to health loss, and remains the leading cause of global mortality, representing more than 30% of global deaths in 2019 (WHO, 2021). More than 80 % of these deaths are due to coronary heart disease (CHD) and stroke, and over three-quarters of CVD deaths occur in low- and middle-income countries (WHO, 2021). Also, modifiable risk factors for CVD, such as obesity, smoking, diabetes mellitus (DM), hypertension (HTN), dyslipidemia, and low physical activity, are common, and they have been on growth throughout the world (WHO, 2016).

CVD and risk factors are also responsible for a substantial disease burden as they continue to be the principal cause of disease-related disability and premature CV mortality for more than a decade (Raal et al., 2018; WHO, 2015). Indeed, the recent Global burden of CVD and risk factors study reported alarming findings (Roth et al., 2020). For instance, global trends in disability-adjusted life years and years of life lost owing to CVD and its modifiable risk factors have risen dramatically over the last three decades. Similarly, the number of years lived with a disability doubled throughout the same time frame (Roth et al., 2020). Noticeably, CVD causes a heavy burden not only on the patients but also on their families and the governments (Dunbar et al., 2018; Leal et al., 2006; Pattenden et al., 2007; Petch, 2015). Accordingly, prevention and reversing CVD growth is a public health priority.

1.1.2 Epidemiology of Cardiovascular Disease in the Middle East

A total of 22 nations (including Yemen) make up the Eastern Mediterranean Region (EMR), with about 679 million people. Studies done in the EMR showed a high rate of CVD, especially CHD (Turk-Adawi et al., 2018). In 2015, 34.1% of deaths in the EMR were caused by CVDs (Mokdad et al., 2018). Ischaemic heart disease (IHD) is the most common type of CVD, accounting for 49.7% of all CVDs, followed by cerebrovascular diseases (21.8%) (Turk-Adawi et al., 2018).

Moreover, all major risk factors for CVD increased dramatically in the Middle East and North Africa (MENA) region (Traina et al., 2017). In this light, the prevalences of hypertension, hypercholesterolemia, obesity, physical inactivity, and diabetes mellitus are among the highest rates in all WHO-designated geographical regions (Traina et al., 2017; Turk-Adawi et al., 2018). For example, the International Diabetes Foundation (IDF) revealed that the MENA region has the greatest prevalence of diabetes (12.5%) compared to 8.6% in Southeast Asia and 6% in Europe (Whiting et al., 2011). According to the IDF, more than 35 million people in the MENA region had diabetes in 2015, which is anticipated to double by 2040. Additionally, the EMR had a cigarette smoking prevalence of 25.4%, greater than the global rate of 22.7% (Turk-Adawi et al., 2018). Moreover, insufficient physical exercise is more prevalent in the EMR than in other regions (38.7% for women and 27.5% for men). Furthermore, the EMR has the third-highest rate of obesity among all geographical areas (Turk-Adawi et al., 2018).

1.1.3 Prevalence of Cardiovascular Risk Factors in Yemen

Yemen is one of the poorest countries in the EMR region. Yemen's healthcare system is fragile and has many shortcomings, including insufficient and understaffed healthcare facilities, a lack of crucial medical equipment, and the unbalanced distribution of human and financial resources (Qirbi & Ismail, 2017; Zawiah et al., 2020). Moreover, there have been reports of medication shortages and soaring prices in Yemen (Mohamed Ibrahim et al., 2021).

Several health-related indicators in Yemen were reported in the 2018 World Health Statistics (WHO, 2018). In this light, the universal coverage index for essential health services was 39, making it one of the lowest in the world. Furthermore, tobacco smoking is increasing among males aged 15 and older (29.2%). Moreover, the probability of dying from CVD, cancer, and DM between ages 30 and 70 in 2016 was 30.6%, the highest globally. Furthermore, the physician density was 0.3 per 1000 people, one of the lowest in the EMR region. In 2015, government health spending was less than 2.5% of the general government expenditure.

In Yemen, CVD and risk factors burden are prevalent. For example, the CVD mortality rate was 21% in 2017 (Turk-Adawi et al., 2018). Moreover, Yemeni individuals with acute coronary syndrome (ACS) present at a relatively young age with a high prevalence of smoking, khat chewing, and HTN (Ahmed et al., 2013). Yemen had the highest mortality rate among Gulf states in the Gulf Registry of acute coronary syndrome study (Gulf Race-2) (AlHabib et al., 2012). Furthermore, the total prevalence of stroke among patients attending a teaching hospital in Yemen's Dhamar governorate was 6.1 %, and the majority were ischemic strokes (76.9%). HTN and smoking were also found in 57.1% and 47.3% of stroke patients, respectively, and

74.73% of patients reported regularly chewing khat (Salah et al., 2019). Most Yemenis chew khat leaves on a daily basis as a social habit, especially at weddings and funeral gatherings. Furthermore, due to its stimulant properties, schoolchildren and university students chew khat to boost their energy when studying the subjects (Al-Motarreb & Jassim, 2022). Khat (Catha edulis) leaves have been linked to an increased risk of stroke, myocardial infarction (MI), heart failure (HF), and in-hospital mortality (Ali et al., 2010; Mega & Dabe, 2017). Moreover, khat chewers with ACS had worse outcomes (stroke, recurrent myocardial ischemia, death) compared to ACS patients not using khat (Al-Motarreb & Jassim, 2022).

The prevalence rate of metabolic syndrome is also high in Yemen (Ansari-Moghaddam et al., 2019). In Yemeni people aged 20 and older, the prevalence of diabetes was 9.75% (Al-Sharafi & Gunaid, 2014). In DM, dyslipidemia is one of the key risk factors for CVD development, and it is prevalent among Yemeni patients with type 2 DM (68.5%) (Al-Shammakh et al., 2020). Also, a high prevalence of physical inactivity has been reported in the Arab world (Sharara et al., 2018). For instance, 94% of the Yemeni rural females were physically inactive (Alwabr, 2018). These alarming numbers and their anticipated increase in the future put a significant strain on already overburdened healthcare systems in the Arab world (Rahim et al., 2014), especially in Yemen (Zawiah et al., 2020). Therefore, improvements in preventive care and adequate management and knowledge of cardiovascular disease and risk factors are required.

1.2 Cardiovascular Disease Risk Assessment and Prevention

A huge percentage of CVD could be prevented, and the mortality associated with CVD could be decreased by addressing and treating the modifiable risk factors

(Buttar et al., 2005; Lin et al., 2016). Therefore, CV risk assessment, awareness, and management of modifiable risk factors are vital steps in reducing the incidence of these conditions and the resultant disease burden. Prevention of CVD is a multi-interventional approach, and depending on the magnitude of risk; it involves either commencing lifestyle modifications alone or concomitantly with pharmacotherapy (Karwalajtys & Kaczorowski, 2010; Ministry of Health Malaysia, 2017a). Although healthy lifestyle behaviors are important determinants of cholesterol-lowering and CVD prevention, the introduction of pharmacological therapies (namely, statins) has significantly contributed to CVDs reduction (Armitage, 2007; Baigent et al., 2010; Chou et al., 2016; Ramkumar et al., 2016). However, risk evaluation of atherosclerotic cardiovascular disease (ASCVD) must precede statins' prescription for primary prevention of CVD (Arnett et al., 2019). ASCVD includes ACS, stroke, transient ischemic attack (TIA), coronary or other arterial revascularization, stable or unstable angina, peripheral artery disease (PAD), and aortic aneurysm, all of atherosclerotic origin (Grundy et al., 2019).

ASCVD risk assessment remains the cornerstone of primary prevention (Arnett et al., 2019). The ASCVD risk can be assessed using risk estimation algorithms created based on the results of cohort studies (Lloyd-Jones et al., 2019). These risk tools were designed to assist healthcare providers in identifying an individual's risk of CVD and proposing appropriate treatment. Different guidelines recommend different risk score calculators for assessing the 10-year CV risk (Grundy et al., 2019; Mach et al., 2019). These risk calculators differ in the variables included and the endpoints evaluated (Lloyd-Jones et al., 2019; Wilson, 2021). For example, the 2008 Framingham General CVD risk calculator uses the variables of gender, age, total cholesterol, high-density lipoprotein cholesterol (HDL-C), systolic blood pressure, antihypertensive therapy, history of DM, and current smoking status (Lloyd-Jones et al., 2019; Wilson, 2021). The outcomes being assessed are the total CVD (coronary insufficiency or angina, HF, intermittent claudication, CHD death, nonfatal MI, fatal or nonfatal ischemic or hemorrhagic stroke, and transient ischemic attack). The ACC/AHA risk estimator includes almost the same parameters as the 2008 Framingham Risk Score (FRS), but in contrast to the FRS model, it adds the race and measures only hard ASCVD endpoints (CHD death, nonfatal MI, fatal and nonfatal stroke) (Lloyd-Jones et al., 2019; Wilson, 2021).

Currently, the clinical practice guidelines (CPGs) on the management of dyslipidemia and primary prevention of CVD recommend a risk assessment of CVD for eligible patients (Arnett et al., 2019; Grundy et al., 2019). The 10-year cardiovascular risk assessment help to guide decision-making on various preventive measures such as initiating or deferring statin therapy (Arnett et al., 2019). Also, calculating the 10-year ASCVD risk enables the healthcare providers to adjust the intensity of preventive measures with the patient’s risk, optimizing the benefits and mitigating the possible harm. In this light, the 2018 American College of Cardiology and American Heart Association (ACC/AHA) guideline on the management of dyslipidemia recommends that a 10-year risk calculation should be performed for adult patients aged 40-75 years old who are free of ASCVD, DM, and primary hypercholesterolemia before initiating statin therapy as a primary prevention strategy. Also, it advocates for a lifetime risk calculation for younger individuals (Grundy et al., 2019). For patients with DM (40-75 years old), ASCVD, and primary hypercholesterolemia, statin therapy is recommended without risk assessment. However, the ASCVD risk assessment can be used in these conditions to intensify the statin treatment (Arnett et al., 2019).

1.3 Statins

1.3.1 Clinical Pharmacology

Statins lower intracellular hepatic cholesterol synthesis by acting as competitive inhibitors of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA reductase); the rate-limiting enzyme in cholesterol synthesis (Cerqueira et al., 2016). This promotes greater clearance of LDL-C from the blood, resulting in a 20% to 55% drop in circulating LDL-C levels (Buhaescu & Izzedine, 2007). Statins are also effective in lowering triglycerides (TG). The higher the baseline TG level, the larger the % reduction in TG that will occur with statin therapy (Maki et al., 2012), and they can induce a modest increase in HDL-C levels. These positive effects vary depending on the statin (atorvastatin, rosuvastatin, simvastatin, pitavastatin, lovastatin, pravastatin, and fluvastatin), dose intensity (high, moderate, low), and patients characteristics. Patient characteristics include physical activity, diet, body weight, age, gender, non-adherence, and genotypes (Akyea et al., 2019). Atorvastatin and rosuvastatin are significantly more potent than other statin medications. Therefore, equivalent doses for LDL cholesterol lowering should be utilized when switching between statin medicines (Rosenson, 2012). Table 1.1 illustrates the definitions and classifications of statin dose intensity adopted from the ACC/AHA guideline (Grundy et al., 2019).

Table 1.1 The definitions and classifications of statins dose-intensity

High-intensity statin Lower LDL by ≥ 50 %	Moderate-intensity statin Lower LDL by 30 to <50%	Low-intensity statin Lower LDL by <30%
Atorvastatin 40–80 mg * Rosuvastatin 20–40 mg*	Atorvastatin 10–20mg* Rosuvastatin 5–10mg* Simvastatin 20–40mg Pravastatin 40–80mg Lovastatin 40–80mg Fluvastatin XL 80mg* Fluvastatin 40mg/BID Pitavastatin 1–4 mg*	Simvastatin 10 mg Pravastatin 10 or 20 mg Lovastatin 10 or 20 Fluvastatin 20 or 40mg/day
*Asterisk means this medication can be administered at any time of day due to their long half time		

Adapted from the 2018 ACC/AHA guideline:(Grundy et al., 2019)

1.3.2 Statins Pharmacokinetics

Statins exhibit several pharmacokinetic (PK) variations, including absorption, bioavailability, lipophilicity, half-life, excretion, and metabolism (Cid-Conde & López-Castro, 2020; Damiani et al., 2020; Schachter, 2005). All statins have a fast absorption rate with a peak plasma concentration of two to four hours and a poor blood bioavailability due to high first-pass liver metabolism.

Most statins are metabolized through the microsomal cytochrome P450 (CYP) isoenzymes system. Simvastatin, lovastatin, and to a lesser extent, atorvastatin are metabolized mainly by CYP3A4, whereas fluvastatin, rosuvastatin, and pitavastatin require the CYP2C9 enzyme (Corsini et al., 1999). The primary route of elimination is through the biliary system into the feces, with 5–20% excreted in the urine, except for atorvastatin, which has the lowest renal excretion (less than 2%) (Cid-Conde & López-Castro, 2020). This is why, for people with impaired glomerular filtration rate, atorvastatin is the preferred statin; it can be used without dose adjustment in all stages of chronic kidney disease (CKD) (Wiggins et al., 2016).

The half-lives of simvastatin, fluvastatin, pravastatin, and lovastatin are relatively short, ranging from 1 to 3 hours. To maximize the effect, these statins should be taken at night or use extended-release formulations (e.g., fluvastatin 80mg XL) (Wiggins et al., 2016). On the other hand, rosuvastatin (19-20.8 hours), atorvastatin (14-30 hours), and pitavastatin (12-13 hours) can be taken at any time of day as they have longer half-lives (Cid-Conde & López-Castro, 2020; Schachter, 2005).

1.3.3 Clinical Indications

Statins are the most powerful, widely prescribed, and evidence-based medications in the world for lowering LDL-C levels and decreasing the morbidity and mortality of CVDs (ESU, 2005). There is strong evidence that lowering LDL-C decreases ASCVD (Ference et al., 2017). With every one mmol/L (38.7 mg/dL) drop in LDL-C, the relative risk of major coronary and vascular events is reduced by 22 % (Silverman et al., 2016). Therefore, lowering the low-density lipoprotein cholesterol (LDL-C) levels with statin therapy has become a fundamental goal in preventing and treating ASCVD. Millions of individuals worldwide use statins, and their significant impact on CVD has been established. In this light, numerous clinical trials and meta-analysis studies have shown the considerable effects of statin therapy on reducing major vascular events such as MI and ischemic stroke (Armitage, 2007; Baigent et al., 2010; Chou et al., 2016; Ramkumar et al., 2016).

Due to the overwhelming body of evidence supporting their CV benefits, statins are clinically indicated by all CPGs for primary and secondary prevention of CVD (Grundy et al., 2019; Mach et al., 2019; Ministry of Health Malaysia, 2017a; Stone et al., 2014). In this light, the latest 2018 ACC/AHA multi-society guideline on the management of blood cholesterol provides strong recommendations for initiating statin therapy for patients with ASCVD, DM (40-75 years), and primary hypercholesterolemia (≥190mg /dl). These three groups of patients do not need a risk assessment to initiate statin therapy. The fourth statin-benefit group is individuals aged 40-75 years old, but a 10-year ASCVD risk assessment should be performed for this age category. In this light, for individuals with high risk (>=20%) or intermediate risk (7.5 - <20%) in the presence of risk enhancers, statin therapy should be initiated. Table 1.2 summarizes statins' clinical indications, recommended dose intensity, the strength of recommendation (SOR), and quality of evidence (QOE) based on the 2018 ACC/AHA cholesterol management guideline (Grundy et al., 2019).

Table 1.2 The summary of statins' clinical indications, recommended dose intensity, the strength of recommendation (SOR), and quality of evidence (QOE)

Clinical indication	**Statin intensity**	**(SOR)**	**(QOE)**
ASCVD - ≤ 75 years old - >75 years old	 - High-intensity statin - Moderate- or high-intensity statin (after evaluation of patient’s ASCVD risk, fragility, preference, adverse effects, and drug-drug interactions)	 I IIa	 A B-R
DM patients (40-75 years old)	Moderate-intensity statin (regardless of estimated 10-year ASCVD risk) High-intensity statin (if multiple CV risk factors, age 50-75, ASCVD risk >20)	I IIa	A B-R
LDL≥190mg /dl (20-75 years old)	Maximally tolerated statin therapy or high-intesnsity statin	I	A
10-year ASCVD ≥20% (High risk)	High-intesnsity statin	I	A
10-year ASCVD 7.5-<20% (if intermediate risk with the presence of risk enhancers favors statin)	Moderate-intensity statin	I	A
Risk enhancers include a family history of premature ASCVD, metabolic syndrome, CKD (eGFR 15–59 mL/min/1.73 m2 +/-albuminuria not on dialysis), chronic Inflammatory Conditions (rheumatoid Arthritis, systemic lupus, HIV, female-specific risk factors (history of pre-eclampsia or early menopause before age 40, ethnicity (South Asian ancestry), lipid/risk biomarkers (persistent LDL 160-189 mg/dL, persistent primary TG elevation ≥ 175 mg/dL)			

Adapted from the 2018 ACC/AHA guideline: (Grundy et al., 2019)

1.3.4 Statins Safety

Statin use is considered to be relatively safe. However, no drug is without the possibility of side effects. Statin-associated muscle symptoms (SAMS) are the most common side effects and the most common reason for discontinuation (Abd & Jacobson, 2011; Grundy et al., 2019; Stroes et al., 2015). Myalgia, a type of SAMS, is characterized as muscle pain or soreness with normal or mild creatinine kinase (CK) elevations. In randomized trials, the prevalence of myalgia ranges from 1.5 % to 5% (Law & Rudnicka, 2006; Silva et al., 2006). However, the prevalence is much higher in observational research and clinical experience, ranging from 7 % to 29% (Stroes et al., 2015). Another rare but serious muscle-related side effect is rhabdomyolysis which is defined as an elevation in the muscle enzyme CK of >10x upper limit normal (ULN) with renal injury (Grundy et al., 2019).

The etiology of the symptoms is not well-understood. However, several predisposing factors have been highlighted in the literature, including old age, female gender, genetic factors, prior myopathy, thyroid diseases, impaired liver or kidney function, a high-intensity statin, and statin-drug interactions (Banach et al., 2015; Grundy et al., 2019; Muntean et al., 2017; Ward et al., 2019). Healthcare providers' knowledge of potential adverse effects and predisposing factors is vital so that routine monitoring can be explicitly targeted to risk populations.

Statins are associated with other serious side effects. For example, the use of statins has been linked to a modest increase (12%) in the risk of developing diabetes in a network meta-analysis of randomized controlled trials (RCTs), and the highest risk was associated with the use of high-intensity statins, particularly atorvastatin 80mg followed by rosuvastatin (Thakker et al., 2016). The risk of new-onset DM following statin therapy could be more frequent in the presence of other predisposing factors such as A1c ≥ 6%, metabolic syndrome, fasting glucose ≥ 100 mg/dL, or body mass index (BMI) ≥ 30 (Grundy et al., 2019). Other infrequent side effects that have been reported with statin therapy include liver toxicity, fatigue, insomnia, and peripheral neuropathy (Mancini et al., 2011). In addition, neurocognitive symptoms were highlighted in case reports and observational studies (Hammad et al., 2019a; Suraweera et al., 2016). RCTs, on the other hand, reported no increase in memory/cognition issues (Ott et al., 2015). In contrast, two meta-analysis studies reported that statin use is associated with a lower risk of mild cognitive impairment and dementia (Chu et al., 2018; Poly et al., 2020). This difference in results could be due to different methodological approaches and study settings. For example, some of the studies are case reports and observational studies, while others are meta-analsyses of prospective cohort studies or RCTs.

1.3.5 Safety and Efficacy Monitoring Parameters

1.3.5(a) Lipids monitoring (LDL-C)

The main reason for cholesterol monitoring during statin treatment is to determine whether treatment goals have been met. Although the exact goal values are still up for controversy, most guidelines (Arnett et al., 2019; Board, 2014; Duerden et al., 2015; Grundy et al., 2019; Mach et al., 2020; Members et al., 2016; Pearson et al., 2021) take a similar approach to identifying and establishing targets, with LDL-C values being the primary therapeutic target for initiating and adjusting lipid-lowering treatment (Wang & Liang, 2020). The rationale behind this is that LDL-C plays an essential role in the etiology and progression of ASCVD. In addition, elevated LDL-C levels are linked to an increased risk of CVD events, whereas reducing LDL-C levels results in a decrease in events (Ference et al., 2017). Accordingly, the LDL-C specific target or % reduction is adapted to the overall CV level of risk in major guidelines with a lower threshold for patients having very high ASCVD risk (Grundy et al., 2019; Mach et al., 2020). Following that, a lipid panel should be taken before initiating statin therapy. Then, lipids should be evaluated 4-12 weeks following statin commencement, dose adjustment, or add-on therapy. After that, patients who have met their therapy goals may need to be monitored every 3-12 months or as clinically indicated (Grundy et al., 2019).

1.3.5(b) Creatinine kinase monitoring

Along with symptoms, CK elevation is usually used for detecting severe myopathy. However, CK elevations can be induced by various reasons, including vigorous physical activity and hypothyroidism (Newman et al., 2019). Therefore, other causes must be ruled out before statin-induced myopathy is diagnosed. Given the rarity of CK increases associated with statin medication, the lack of established cost-effectiveness, and the unlikely impact on clinical outcomes, routine CK monitoring is not recommended anymore by major guidelines (Grundy et al., 2019; Mach et al., 2020; Stroes et al., 2015). Nevertheless, any patient presenting with unexplained muscle complaints should have their CK levels checked. Failure to do so can result in a missed diagnosis of myopathy, which can develop into rhabdomyolysis and kidney injury if the statin is not discontinued (Newman et al., 2019). Herein comes the importance of counseling patients about the potential side effects and instructing them to report any significant muscle symptoms.

1.3.5(c) Liver Enzymes monitoring

Statins tend to cause asymptomatic dose-dependent transaminase elevations (>3 ULN), and this by itself does not imply severe liver damage (Newman et al., 2019). Previously, CPGs recommended that liver function tests be checked before starting statins and regularly monitored after that (Wiklund et al., 2013). The Food and Drug Administration (FDA) and the recent CPGs revised the recommendation for monitoring liver enzymes during statin therapy (Newman et al., 2019). This is because the liver injury caused by statins is exceedingly rare, 1 in 100,000 patients treated with statins was reported to have this side effect (Björnsson et al., 2012), and routine monitoring does not appear to detect or prevent serious liver injury in patients taking statins. According to the updated recommendation, liver function tests should be done prior to statin commencement and as clinically needed afterward rather than routine monitoring (Grundy et al., 2019).

1.3.5(d) Diabetes monitoring

The 2018 ACC/AHA guideline acknowledges the increased risk of new-onset DM among patients taking statins, but there is no clear recommendation regarding routine HbA1c or glucose monitoring. Nevertheless, the guideline recommends continuing statin therapy in individuals with new-onset DM or increased risk as the benefits outweigh the risks (Grundy et al., 2019).

On the other hand, the 2019 European Society of Cardiology/the European Atherosclerosis Society (ESC/EAS) guideline and the 2017 Malaysian CPGs have more explicit recommendations regarding HbA1c or glucose monitoring. The 2019 ESC/EAS guideline recommends that regular HbA1c or glucose testing should be considered in patients at high risk of developing diabetes and on high-dose statin therapy (Mach et al., 2020). Similarly, the 2017 Malaysian clinical practice guideline recommends that diabetes screening be considered every 6 to 12 months in patients at high risk of acquiring diabetes (Ministry of Health Malaysia, 2017b). As defined by both guidelines, high-risk individuals include patients with metabolic syndrome, signs of insulin resistance or obesity, the elderly, and patients with a family history of DM (Mach et al., 2020; Ministry of Health Malaysia, 2017b).

Table 1.3 A summary of the key difference between the latest clinical practice guidelines concerning monitoring parameters for statin therapy

Recommendations	**Clinical practice guidelines**		
	AHA (2018)	**ESC/EAS (2019)**	**Malaysian (2017)**
Baseline: before statin therapy initiation			
Lipid levels	✓	✓	✓
Liver enzymes	✓	✓	✓
CK		✓	
Follow-up: 4–12 weeks after starting a statin therapy or after a dose change.			
Lipid levels	✓	✓	✓
Liver enzymes		✓	✓
CK		✓	
Routine measurement			
Lipid levels	✓ (3-12 months)	✓ (Annually)	✓ (at 6 to 12 month Intervals)
Liver enzymes	Not recommended	Not recommended	Not recommended
CK	Not recommended	Not recommended	Not recommended

1.3.6 Contraindications

The general contraindications for all statins include active liver disease, unexplained persistent elevations of serum transaminases; pregnancy; and breastfeeding (McIver & Siddique, 2021).

1.4 Drug-Drug Interactions

A drug-drug interaction (DDI) is described as a pharmacokinetic (PK) or pharmacodynamic (PD) effect of one drug on another that differs from the known or predicted effects of each agent taken on its own (Wiggins et al., 2016). Clinically relevant DDI usually changes the efficacy or safety of one or both interacting drugs (Becker et al., 2005). When one medicine changes the pharmacological activity of another in an additive, synergistic, or antagonistic manner, this is referred to as a PD DDI. PK DDIs, on the other hand, cause changes in the medication's absorption, distribution, metabolism, or excretion (Wiggins et al., 2016). Inhibition or induction of medication metabolism and/or transport causes the majority of clinically significant DDIs (Bellosta & Corsini, 2012).

DDIs represent a serious clinical issue that must be addressed. DDIs account for around 15% of all avoidable prescription errors in the clinical setting (Damiani et al., 2020). Also, DDIs significantly raise the likelihood of adverse side effects, which can be severe enough to necessitate hospitalization. DDIs have been reported to account for up to 2.8% of hospital admissions. However, as many drug-related problems are typically reported as adverse drug reactions (ADRs), the true prevalence of hospitalization due to DDIs is probably underreported (Wiggins et al., 2016).

Complex underlying diseases can also make it more difficult to recognize a DDI, contributing further to a lower reported incidence. A DDI can have a wide range of clinical effects, from minor to life-threatening conditions, depending on drug-specific and patient-specific factors (Wiggins et al., 2016). Drug-specific aspects include the PK properties of each medication (e.g., half-life, binding affinity, the dose of the drugs, sequence and administration time, serum concentrations, and the duration of concomitant use of interacting medications. Gender, age, genetic polymorphisms, and diseases that affect the metabolism and excretion of medications (liver and kidney diseases) are examples of patient-specific factors (Damiani et al., 2020; Hirota et al., 2020; Wiggins et al., 2016).

1.4.1 Statin-Drug Interactions

It is critical to note that statins are very selective inhibitors of HMG-CoA reductase, with little or no affinity for other enzymes and receptor systems. This reflects that statin medications usually do not interact with other medications at the PD level (Corsini et al., 1999).

The majority of clinically relevant statin-drug interactions (SDIs) are PK-related, and the risk of SDIs differs between statins due to the different PK profiles (Bellosta & Corsini, 2018). The two most frequently encountered pharmacokinetic DDIs involving statins are those related to drug metabolism (the CYP P-450 enzyme system) and transport proteins implicated in statin absorption and excretion, such as permeability glycoproteins (P-gp) and organic anion-transporting polyprotein (OATP1B1) (Wiggins et al., 2016). P-gp, also known as multidrug resistance-1 (MDR1), limits oral absorption and stimulates the substrate secretion into urine and bile, and OATP1B1 is engaged in the hepatic uptake of statins (Bellosta & Corsini, 2018; Wiggins et al., 2016). Also, genetic polymorphisms affecting the CYP enzyme and transport proteins may contribute to SDIs (Arrigoni et al., 2017). Blocking the enzymes responsible for statins' metabolism and transport usually results in higher serum statin concentrations. In this light, systemic statin exposure may be increased by medications that inhibit CYP enzymes or interfere with statin transporters (Bellosta

& Corsini, 2018; Wiggins et al., 2016). Therefore, when choosing a statin for a patient, it is critical to assess the potential SDIs, considering the statins' various PK properties.

1.5 Adherence to Medications

1.5.1 Definitions

A variety of terms, such as adherence, persistence, concordance, and compliance, are used to describe the action of obtaining prescriptions and taking the medications as prescribed. It is common to use these terms interchangeably, yet they have different views about the patient-healthcare provider relationship (Vrijens et al., 2012). The term compliance was coined and defined for the first time in 1976 by Haynes (Haynes et al., 1979). It describes “the extent to which a person's behavior (in terms of taking medication: following diets or executing other lifestyle changes) coincides with medical or health advice” (Haynes et al., 1979; Vrijens et al., 2012). On the other hand, adherence was defined in 2003 by the WHO as “the degree to which the person’s behavior corresponds with the agreed recommendations from a health care provider" (WHO, 2003). In contrast to compliance, which negatively implies that the patient is passively following the phyician's orders, the term adherence implies that the treatment plan is based on the patient-physician agreement (Osterberg & Blaschke, 2005). Therefore, adherence is currently a more prefered term, and it is more commonly used in the literature.

Concordance is a newer concept that emphasizes the relationship and interaction between the patient and the prescriber and the extent to which the therapy represents a mutually agreed decision (Vrijens et al., 2012). The concordance also implies that patients should be fully involved in therapeutic decision-making and bear a higher responsibility for their care (Aronson, 2007).

A newer taxonomy for adherence was established by Vrijens et at. in 2012 (Vrijens et al., 2012) that involves three crucial steps: initiation (the point at which the patient takes the first dose), implementation (the extent to which the prescribed treatment plan is fulfilled), and discontinuation (when a patient stops taking medication). Persistence is defined as the time interval between initiation and discontinuation (Cramer et al., 2008). So, a weak persistence refers to a patient who stopped taking his medication earlier than prescribed. Another term associated with adherence is primary non-adherence, a condition when a patient receives a prescription for a new prescription but does not fill it (Raebel et al., 2013).

In this study, the term "adherence" was used to reflect the patients' adherence to statin therapy. This is because this term is more commonly used in statin adherence assessment studies compared to other terms, as shown in section 2.4. More importantly, it is the same term that is utilized in the medication adherence rating scale that we have utilized in this study.

1.5.2 Factors Affecting Medication Adherence

The reasons why patients do not take their medications are complicated and vary from person to person. Knowing the reasons for non-adherence allows for a proper intervention to be tailored to each patient's particular needs. According to the WHO and the International Pharmaceutical Federation (FIP), adherence to long-term treatment therapies is approximately 50% in developed countries. The figure is much lower in developing countries due to disparities in access to healthcare facilities and suboptimal supervision by healthcare providers (FIP, 2003; WHO, 2003). Medication adherence is a multifaceted and complex behavior. Indeed, the literature has described various factors that influence patients' adherence. Patients may fail to take their medications as prescribed for various reasons, including forgetfulness, a lack of knowledge, and even emotional issues (Osterberg & Blaschke, 2005). Other reasons for non-adherence include adverse effects, the asymptomatic nature of the disease (e.g., HTN, dyslipidemia), the cost of the copayment, polypharmacy, low socioeconomic status and financial concerns, the absence of prescription drug coverage, the complexity of the treatment regimen, and a poor patient-provider relationship (Polinski et al., 2014; WHO, 2003).

There are also other reasons why people do not take their medications, such as beliefs about the source of illnesses, high costs of medications, long distances to treatment, limited drug supplies, and low health literacy (Kini & Ho, 2018). Other factors include poorly developed healthcare services, lack of knowledge and training for healthcare providers regarding the management of chronic diseases, and inadequate or non-existent reimbursement by health insurance plans (Gast & Mathes, 2019). Due to these factors, LMICs would be expected to have lower levels of medication adherence.

1.5.3 Implications of Non-Adherence

Poor adherence to medications negatively influences health outcomes (Ogungbe et al., 2021). In this light, an increase in hospitalizations, adverse effects, and mortality risk has been linked to medication non-adherence (Ho et al., 2009). Moreover, adherence to prescriptions is critical for lowering total healthcare costs. Furthermore, poor drug adherence was associated with increased healthcare costs. In the United States, between 33% and 69% of medication-related hospital admissions are attributable to poor adherence, at the cost of nearly $100 billion every year

(Osterberg & Blaschke, 2005). Similarly, poor medication adherence is responsible for about 9% of all CVD incidents in Europe (Chowdhury et al., 2013).

The use of cardiovascular drugs for an extended period of time is associated with a significant reduction in the risk of morbidity and mortality (Kim et al., 2016). However, the full therapeutic effect of these medications cannot be obtained if patients have poor adherence (Nunes et al., 2009). In this light, non-adherence to statin therapy raises the risk of developing CV events or death compared to adherent patients (Rublee et al., 2012). Moreover, in a population-based cohort study of Swedish type 2 diabetes patients (Karlsson et al., 2018), increased statins refill adherence was linked to a decreased risk of CVD, and the risk of mortality increased with non-persistence. Similarly, low adherence to statin therapy was associated with a greater risk of dying among patients with established ASCVD (Rodriguez et al., 2019). In addition, MI individuals with poor adherence were shown to have a four-fold increased risk of ACS and a two-fold increased risk of CVD hospitalization (Kubica et al., 2015).

On the other hand, better outcomes are achieved when drug regimens are followed (WHO, 2003). For instance, adherence to guideline-recommended treatments was linked to a lower risk of major adverse cardiovascular events and cost savings in a three-year longitudinal analysis of post-MI patients (Bansilal et al., 2016). Therefore, developing strategies to combat medication non-adherence is crucial for enhancing clinical outcomes.

Medications are essential in the therapy and control of CVD. Nevertheless, approximately 30–50% of individuals with chronic conditions do not take their medications as directed (Briesacher et al., 2008). It is much more challenging to adhere to medications in lower-income and war-affected countries such as Yemen, where there is a lack of health resources and social and economic hurdles (Mills et al., 2016; WHO, 2003). Therefore, it is fundamental to assess statin therapy adherence, evaluate its barriers and identify individuals who are not likely to adhere to their statin prescription in order to implement appropriate interventions. In Yemen, these topics have not been explored yet.