

QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCES

THE PREVALENCE OF STATIN PRESCRIPTION FOR PRIMARY
PREVENTION OF ARTERIOSCLEROTIC CARDIOVASCULAR DISEASE
AMONG PATIENTS WITH TYPE 2 DIABETES IN QATAR

BY

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ABSTRACT

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Title: The Prevalence of statin prescription for primary prevention of arteriosclerotic cardiovascular disease among patients with type 2 diabetes in Qatar

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Background: Qatar has one of the highest prevalence rates for diabetes in the world. Arteriosclerotic cardiovascular diseases (ASCVDs) are responsible for nearly 50% of deaths among patients with diabetes in Qatar. Treating with statins is a simple and effective approach for preventing ASCVD among patients with diabetes. Local and international guidelines recommend the use of statins for primary prevention of ASCVD in patients with diabetes, especially for those 40-75 years of age. Yet statins are still under-prescribed to diabetic individuals for primary prevention of ASCVD worldwide, especially in primary care settings which is where most of the medical management of diabetes occurs. Little is known about the prevalence of statin prescription for primary prevention of ASCVD among diabetics in primary care settings in Qatar.

Objectives: To measure the proportion of T2dm patients receiving statins for primary prevention of ASCVD in primary care settings and to investigate patients' characteristics associated with statin prescription.

Methods: A cross sectional review of electronic medical records of patients with T2dm 40-75 years of age, treated in any of the 27 health centers operated by Primary Healthcare Corporation, the largest primary care provider in the country, during calendar year 2019. A multivariable logistic regression model was used to estimate the

odds of being prescribed statins and to adjust for confounding variables.

Results: Of 23,934 patients with complete data, 57% were males and 31.9% were Qatari nationals. Average age for participants was 54.8 ± 8.25 years. 66 % of the patients received statins at least once during the year 2019. The statin prescription rate for Non-Qatari males was 70.1% and was significantly higher than non-Qatari females, Qatari females, or Qatari males (62.2%, 62.9% and 63.9% respectively P value <0.000)

In a multivariable model analysis and after controlling for other covariates in the model, statin prescription was positively associated with being male (adjusted odds ratio (aOR): 1.2, [95% CI: 1.12-1.28]), history of smoking, i.e. former smoker (aOR 1.16 [95% CI: 1.03-1.29]), current smoker (aOR 1.11 [95% CI: 1.01-1.22]), associated diagnosis of hypertension (aOR 1.51 [95% CI: 1.41-1.61]), being prescribed other non-statin lipids lowering medications (aOR 1.44 [95% CI: 1.27-1.63]), increased age (aOR 1.03/year [95% CI: 1.026-1.034]), increasing daily pill burden (aOR 1.23/pill [95% CI: 1.21-1.25]), increasing number of daily medication injections (aOR 1.29/injection [95% CI: 1.23-1.35]), and frequent visits to GP clinic (aOR 1.22/visit [95% CI: 1.19-1.24]). Statin prescription was negatively associated with having a history of diabetic neuropathy (aOR 0.87 [95% CI: 0.75-1.0]), increasing BMI (aOR 0.996/unit [95% CI: 0.9892-1.00]), being Qatari (aOR 0.87 [95% CI: 0.81-0.93]) or being prescribed an anti-platelet (aOR 0.96/unit [95% CI: 0.89-1.03]). Significant negative effect modification between hypertension and either male gender or Qatari nationality was found, further lowering the odds for Qatari males.

Conclusion: Prevalence of statin prescription for primary prevention of ASCVD among patients with T2dm was suboptimal in primary care settings in Qatar and need to be improved. Factors associated with a lower prevalence of statin prescription

namely female gender and Qatari nationality needs to be addressed. Further studies are needed to explore causes of the low prescription rates of statins in Qatar.

DEDICATION

*To my respected parents for all their prayers and care and for making me the person I
am!*

To my loving wife for her support and patience!

To my children for being the joy of my life !

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CHAPTER ONE: INTRODUCTION

1.1 Burden of non-communicable disease in the Eastern Mediterranean region

Noncommunicable diseases (NCDs) like heart disease, stroke, cancer, diabetes, and chronic lung disease are a huge burden to healthcare and a major cause of morbidity and mortality worldwide (1). Diabetes is the most prevalent of all NCDs globally (2). In the Eastern Mediterranean region about half of the people with NCDs die prematurely before the age of 70 years mainly due to cardiovascular diseases (CVDs) accounting for 2.2 million annual deaths (1,2). Arteriosclerotic cardiovascular diseases (ASCVDs) like myocardial infarction (MI) or strokes are the leading cause of CVD deaths. It has been reported that this is a result of multiple risk factors that interplay with genetics resulting in clinical disease (3,4). While some risk factors for ASCVDs are non-modifiable such as increasing age, male sex, family history of ASCVDs or ethnicity, many of the other risk factors including sedentary lifestyle, obesity, smoking, high levels of low density-lipoproteins (LDL) and cholesterol, poorly controlled hypertension, and Type 1 or 2 diabetes mellitus (T1dm or T2dm) are manageable (5-8). Thus, ASCVD is considered to be one of the most preventable causes of death.

The Africa Middle East Cardiovascular Epidemiological (ACE) study demonstrated that CVD risk factors such as obesity, diabetes, hypertension, and smoking are quite prevalent in the region especially in high income Middle Eastern countries where more than 30% of the patients without CVD had four or more CVD risk factors (9) particularly in females (10).

1.2 Diabetes and ASCVD in Qatar

Qatar is an Arabian Gulf state with a total population of around 2.9 million (11). More than a million are Asian migrant workers (12). With one of the most advanced healthcare systems in the world, Qatar's health expenditure per capita was one of the highest in the region and the world in the year 2018 (13). In 2017 Qatar had an estimated 259,200 cases of diabetes with varying estimates of prevalence among adult populations from 14 to 23 %, placing Qatar in the top 10 in diabetes prevalence globally (14,15).

Together, CVDs and diabetes are responsible for nearly 50% of mortality in individuals older than 18 years of age in Qatar (16,17). Further, ASCVD deaths are responsible for about 50% of deaths among patients with diabetes in Qatar (7). The incidence of MI among the adult population in Qatar has been reported to be higher than other Middle Eastern countries (18). This could be due to the high prevalence of ASCVD risk factors among Qatar's population (14,15) and due to the fact that about a third of Qatar's population is composed of Asian migrant workers who tend to have twice as many strokes and coronary events compared to Caucasians and at 5 to 10 years younger (19).

A study investigating the relationship between diabetes and MI in Qatar reported that history of diabetes was found in 40% all patients admitted with acute MI and in 70% of Qatari patients in particular. Further having diabetes increased the risk for MI by six-fold among Qatari nationals and by four-fold among all non-Qatari expats (18).

1.3 Diabetes in primary care in Qatar

The availability of primary health care service is considered to be the “most effective health care delivery method and is integral to a sustainable health care system” (20). It is here where most of the medical management of diabetes occurs (21).

The Primary Healthcare Corporation (PHCC) is a government owned primary health care provider. It was established in 1978 and it is the largest primary care provider in the country. The PHCC offers free and subsidized comprehensive patient centered services to registered patients through 27 centers distributed throughout Qatar. According to Qatari legislation, Qatari nationals can utilize all PHCC services without the need to pay while expats have to co-pay nominal fees for medications (13,22). In 2019, 55,515 patients with diabetes were registered at PHCC. A total of 150,000 diabetes related visits, accounting for 5.0 % of the total consultations were delivered by PHCC in year 2019 compared to 1.2% in 2013, probably reflecting the increased prevalence of diabetes and possibly improved accessibility to PHCC services (23,24).

1.4 Rational for the study

With such a high prevalence of T2dm and the high impact of T2dm on the incidence of CVD and death (18), the Qatar national health strategy (2018-2022) set a goal to reduce the burden associated with NCDs and CVDs by adopting a healthier life style and by including health as a priority in every policy (5,7). Further evidence-based national guidelines for management of NCDs and prevention of ASCVD were developed in collaboration between the Ministry of Public Health (MOPH), Hamad Medical corporation (HMC) and PHCC (16,25).

The aims of care in patients with diabetes include not only blood glucose control but also extend to prevention of diabetes associated complications (e.g., small vessel disease or microvascular complication and ASCVD). The long-term goal is to improve the quality of life and prolong longevity. The focus on glucose control is no longer enough to achieve these goals (26,27).

In 2013 the American College of Cardiology and the American Heart Association (ACC/AHA) updated their recommendations regarding initiation and maintenance of statins for the prevention of ASCVD based on the strong evidence of statins being efficacious and safe (28). The updated recommendations departed from the previous approach of LDL level-based treatment recommendations and defined high risk “benefit groups” who should receive statins as part of ASCVD risk reduction strategies. According to this updated guideline, patients with diabetes who are 40 to 75 years of age should be offered statins irrespective of baseline cholesterol level (3). Later in 2016 and considering the evidence and importance of the issue, both MOPH and PHCC updated their guidelines for the prevention of ASCVD in patients with T2dm and embraced the 2013 ACC/AHA recommendations regarding initiation or continuation of statins for primary prevention of ASCVD in patients with diabetes (4,6,25).

The application of evidence-based guidelines is one way of translating evidence into practice and facilitates the delivery of the best patient care and improvement of patient outcomes (29), yet despite evidence of the effectiveness of statins in preventing ASCVD, they are still under-prescribed to individuals for primary prevention of ASCVD worldwide, especially among patients with diabetes. There’s also wide variability in the rates of prescription and multiple factors affecting the prescription of statins such as patient’s age, sex, and associated comorbidities (30-33).

The use of quality indicators such as rates of prescription of statins has been associated with improved outcomes in diabetic patients. Danish researchers reported that patients being treated by practices with the lowest statin prescription rates had higher reported incidences of new onset CVD and all-cause mortality compared to patients being treated by practices with the highest prescription rates (34).

Little is known about the rate of statin prescription for primary prevention of ASCVD in patients with T2dm in Qatar's primary care settings. To our knowledge no information is currently available regarding the associated attributes of patients and the prescription of statins in PHCC settings. To provide insight into this important aspect of patient care, this study conducted a retrospective review of charts from T2dm patients in order to quantify the rates of statin prescription and to explore patients' attributes associated with statin prescription. This study should help to identify missed opportunities for ASCVD primary prevention using statins in T2dm patients, in line with the Qatar national health strategy 2018-2022.

1.5 Objectives

The main objectives of the study were:

- A. To measure the proportion of T2dm patients receiving statins for primary prevention of ASCVD in PHCC.
- B. To investigate patients' characteristics associated with statin prescription.

1.6 Research Questions:

The current study aimed to answer two main questions:

- A. What is the proportion of T2dm patients who were prescribed statins for primary prevention of ASCVD?

B. What are patients' characteristics associated with statin prescription?

CHAPTER TWO: LITERATURE REVIEW

2.1 ASCVD primary preventive strategies in patients with diabetes:

ASCVD is a product of multiple risk factors that interplay with genetics to produce a clinical CVD (3) Primary prevention of ASCVD can be described as an intervention that prevents the onset of clinical ASCVD (6). Smoking cessation, lowering LDL-cholesterol, or control of high blood pressure have been shown to be the most successful as single preventive interventions, however, multiple risk factor management strategies were even more successful, especially in patients with diabetes (26,35). Proper risk factor assessment and management should therefore result in significant reductions of the incidence and severity of ASCVD, especially in patients with diabetes (3,8,36).

2.1.1 Hypertension and control of blood pressure

Patients with diabetes and coexistent hypertension are at increased risk of diabetes related complications and death compared to normotensive diabetic patients (26,35). Maintaining blood pressure below 140/90 is advisable in most patients with diabetes. This can be achieved, in addition to lifestyle modification, by prescribing pharmacological agents to achieve the desired goal (4,26).

The UK Prospective Diabetes follow up study demonstrated that in patients with T2dm reducing systolic blood pressure by 10 mmHg from a baseline of ≥ 150 mmHg was associated with an 11% reduction in the incidence of MI (37). More recently, a meta-analysis of 49 trials including 73,738 patients showed a more pronounced effect of blood pressure control leading to a 26% reduction in the incidence of MI especially if baseline systolic blood pressure was > 150 mmHg (38). Yet maintaining blood pressure

control often requires more intensive treatment plans over time with multiple anti-hypertensive medications to achieve proper blood pressure target (39).

2.1.2 Smoking cessation

In patients with T2dm, smoking increases the risk of ASCVD by 40-50% and the risk of death by 50% compared to non-smokers (40,41). Smoking cessation is the most effective single strategy to prevent ASCVD (35). It leads to better glucose control, improved blood lipid profile, and ultimately reduction in mortality related to diabetes (41,42). Despite this observation there is no agreed best practice approach to smoking cessation. Many clinical practice guidelines recommend smoker patients and especially those with diabetes or established CVD to stop smoking (6,26,36). However, only few smokers have been shown to successfully quit long term even with medical interventions (43).

2.1.3 Glycemic control

An increase of 1% in glycated hemoglobin (A1c) level above 6.0 % for a mean follow up period of 2.4 years was associated with an 8% increase in CVD incidence (44). Most guidelines agree that attaining an A1c level of $\leq 7\%$ is recommended for most patients with T2dm if it can be achieved safely (6,26,36). Yet attaining a target A1c of $\leq 7\%$ had little effect on the reduction of incidence of CVD and added no extra benefit when combined with either blood pressure control or cholesterol reduction strategies (45). A 1% reduction in A1c from a baseline of 8% needs between 5 to 8 years to show a clinically meaningful effect on ASCVD compared, for example, to statins which show their effect as early as 1 year after treatment (46). Overall, glycemic control plays a relatively small role in the primary prevention of ASCVD in patients with T2dm unlike the evident effect of glycemic control on reducing the incidence and severity of

microvascular complications of diabetes (26). However, the use of newer treatment agents for diabetes such as glucagon-like peptide-1 receptor agonists or sodium-glucose cotransporter 2 inhibitors have been associated with a 12% reduction in CVD mortality and a 12% reduction in MI respectively (47,48). Both drugs are currently recommended for treatment of T2dm in patients with established or at high risk of ASCVD (26,49).

2.1.4 Anti-platelet agents

Anti-platelet agents like aspirin and clopidogrel prevent ASCVDs by inhibiting platelet aggregation thus preventing vascular blockage. Anti-platelet therapy has a well-established role in the secondary prevention of ASCVD (3,27). The use of anti-platelet therapy in the primary prevention of ASCVD has been debated due to a high propensity for these agents to cause major side effects like gastrointestinal bleeding and hemorrhagic strokes while providing minimal protection particularly among patients with diabetes (50). However, some diabetes management guidelines still advocate the use of anti-platelet agents in patients with T2dm who have high risk of ASCVD (3,6,26).

2.2 Statin therapy

People with T2dm have a higher prevalence of abnormal blood lipids like reduced High density lipoprotein (HDL), high triglycerides, and denser more atherogenic LDL particles compared to people without diabetes (3,49). Such blood lipid abnormalities have been well established as playing a role in the pathogenesis of ASCVD (26).

Statins are a group of medications that lower blood cholesterol by inhibiting hepatic 3-hydroxy-3-methyl-glutaryl-coenzyme-A reductase enzyme, a key enzyme in the metabolic pathway of cholesterol production. Lowering cholesterol decreases

subendothelial deposition of the “atherogenic cholesterol” while minimally reducing triglycerides (51) and thus deters or prevents a key step in ASCVD pathogenesis (49). Statins are classified according to their potency into low, moderate, and high intensity statins based on their ability to lower LDL-cholesterol from baseline by <30%, ≥ 30-50% and > 50% respectively (3,49).

2.2.1 Efficacy of statins in primary prevention of ASCVD in patients with diabetes

In patients with diabetes, each 1 mmol/L reduction in LDL cholesterol using statin treatment was associated with a 13% reduction in CVD mortality compared to placebo. This effect was similar in magnitude irrespective of the patient’s gender, body mass index, blood pressure level or history of smoking (28). These effects were consistent with risk reduction seen in statin treated high risk patients without diabetes such as patients with previous MI (52).

A meta-analysis of 7 randomized controlled trials including 12,700 patients with diabetes and without established ASCVD showed a 21% reduction in major adverse cardiovascular events in statin users compared to non-users (53). Similar findings were reported in a meta-analysis of four trials including more than 10,000 diabetic patients, where statin users had a 25% reduction in patients having the first occurrence of a major cardiovascular event (8). Positive statins treatment was associated with a 23% relative risk reduction of all-cause mortality and CVD events among patients with diabetes (54) compared to placebo. Statins were also more effective than either blood pressure control or the use of aspirin (an anti-platelet agent) in primary prevention of ASCVD (RRR 25%, 16% and 10 % respectively) (55).

The number needed to treat for five years (NNT5) in all patients with diabetes was 49, however, when stratified by their ASCVD risk NNT5 would be 25 for T2dm patients

with a high ASCVD risk e.g. older patients with comorbidities and 75 for low-risk T2dm patients (56). NNT has been debated to be higher by 15-25 % than what was originally reported in randomized controlled trials (57).

2.2.2 Efficacy of statins in females

Diabetes seems to attenuate the protective effect of the female sex against the occurrence of CVD (58). Diabetic females have twice the occurrence of mortality from MI compared to diabetic men or non-diabetic females with a history of previous MI (59). Diabetic females have about a 50% relative risk increase in CAD incidence, cardiac death, and all-cause mortality compared to diabetic men (60). Researchers argue that the excess CVD mortality among females is not just due to physiological differences (e.g. smaller coronary vessel caliber compared to men or higher levels of thromboxane A₂, a substance that increases blood coagulability) or different clinical presentations, but also is the result of women's public health being skewed towards maternal and child health as well as a focus on early detection of cancers. Furthermore, evidence of efficacy of statins in primary prevention of ASCVD in females is questioned as females were under-represented in most studies. Current literature has reported varying results among females treated with statins for ASCVD prevention from null effect or only reductions of ASCVD incidence, but not mortality to studies reporting reduction in both incidence and mortality (61).

2.2.3 Safety of statins

Statin use had been feared because of possible association with new onset of dementia, cancer, or increased risk of hemorrhagic strokes, aside from other biochemical or musculoskeletal side effects (62,63).

Compared to placebo, the incidence of aforementioned side effects was not higher in the general population or in patients with diabetes (49). Concerns about cognitive decline or dementia have been rejected by the American Food and Drug Administration (64). The minimal increased risk of hemorrhagic strokes after ischemic strokes reported in the SPARCL trial (62) was largely refuted by the recent findings of another study reporting lower risk for both ischemic and hemorrhagic strokes as early as 6 months of statin use post 1st stroke. This risk reduction persisted and became more evident with continued use (65). Overall, considering the evidence of safety and efficacy, added to simplicity of once daily dosing, these negative effects of statins are outweighed by the ability of statins to prevent more vascular events in the same number of patients (56,66), making treatment with statins a very attractive preventive strategy.

2.3 Prescription rates of statins for primary prevention of ASCVD, a global overview

The issue of under prescription of statins to eligible patients is reported in many parts of the world. Statin prescription for the primary prevention of ASCVD in patients with diabetes has been reported in about 80% of patient aged 40-75 years in Malaysia (67,68), 68 % of veteran diabetic males aged 40-75 in the USA (69), 68% in Scotland (70) 67% in the Netherlands (71) 66% in patients 40-75 years in the UK (72) 56.4 % in Kuwait (73), 55% in Ethiopia (74), 55% in India (75), 47% in Sweden (76), 45% in South Africa (77), 43 % in Turkey (78), but is only 18.5 % in Germany (79).

2.4 Factors associated with statin prescription

Factors related to statin prescription are complex and multiple in the medical literature. Studies reporting on statin prescription described a range of patient related factors, physician related factors across to clinical guidelines and affordability related factors

(31,33,80). Moreover, when it comes to the relationship of diabetic patients' attributes who are prescribed statins for primary prevention of ASCVD studies were not uniform in their results. The multiplicity and variability of the reported results is due to differences in the study design, the studied population, the surveyed risk factors or the examined outcomes in the different studies.

Most researchers agree with the clinical evidence that statin prescription for primary prevention of ASCVD in patients with T2dm is positively associated with increasing patient age (33,69-71,74,76), the presence of diabetic complications (69,76,77), coexisting hypertension (74,76,79) and a history of smoking (70,76,79). This agreement is not the case when it comes to the association of female sex with statin prescriptions. Women at high risk for ASCVD in Australia and India were less likely to get guideline recommended preventive medications like statins (75,80). This gender disparity was the opposite in Sweden and Ethiopia (74,76). Researchers in the UK found that gender had no bearing on prescribing statins to patients. They also reported a consistent increase in the chances of being prescribed statins for the primary prevention of ASCVD among females between the ages of 45 and 75 years (81). Findings of gender neutrality in statin prescription have also been reported in Scotland (70), South Africa (77) and Netherlands (71).

Affordability of statin medication has also been reported to be a barrier to statin prescription (82). Free or subsidized statins were associated with increased statin use in the general population in high income countries (83). This was not the situation for people with diabetes in some low-income countries (74). Some studies related lower rates of statin prescription in the general population to be associated with lower socioeconomic status (33); however, few studies have reported on the relationship between affordability or socioeconomic status and statin prescription among patients

with diabetes (74,77). This is despite that cost efficiency of statins in primary prevention of ASCVD has been established across different populations (66,84), but not for people younger than 40 years of age and those with lower risk profiles (85,86). Polypharmacy has also been shown to be associated with higher rates of statin prescription (76,87). Polypharmacy can be defined as simultaneous use of five or more medications, although there is no agreed upon definition of polypharmacy. The problem with this definition is that it misses out on the number of tablets being taken by a patient (88), especially in light of the observation that high pill burden was associated with lower medication refill rates in patient with diabetes (89). The chances of polypharmacy in people with diabetes were associated with older age and number of comorbidities (90,91), all of which are related to higher chances of being on statins and possibly reflecting the complexity of the disease due to coexisting comorbidities necessitating increased use of medication (92). In Qatar, polypharmacy was found to affect patient adherence to use and refill of medication (93).

The co-prescription of certain drugs like non-statin lipid lowering drugs such as fibrates, Ezetimibe or Omega-3 fatty acids was also associated with increased chances of statin prescription for primary prevention of ASCVD among patients with diabetes (69,76). Current guidelines suggest the use of these medications when lipid target goals are not achieved by use of maximum recommended or maximum tolerated statin dose or when patients with diabetes are at high risk of ASCVD (3,6,26). Moreover, the absence of other preventive medications like aspirin was associated with lower rates of statin prescription for primary (76) as well as for secondary prevention of ASCVD (94). Lastly, increased number of visits to medical clinics was associated with increased statin prescription rates in the general population as well as in patients with T2dm (69,87). Appendix 1 summarizes key findings of studies reporting on statin prescription

in primary prevention of ASCVD.

CHAPTER THREE: METHODS

3.1 Study design

A cross sectional review of patients' Electronic Medical Records (EMR) Cerner® was carried out. The screening period was for 12 months starting from 1st January 2019 through 31st December 2019.

3.2 Target population

The target population was all PHCC registered T2dm patients during the calendar year 2019. Although the AHA guidelines do not differentiate in statin indication between T1dm and T2dm (3), MOPH and PHCC guidelines and recommendations were published specifically for T2dm patients (4,6,25).

3.3 Clinical guidelines

The sources of guidelines for this study were PHCC and MOPH guideline documents (4,6,25). For the main objective of this study, it stated that for primary prevention of ASCVD in patients with T2dm and in the absence of contraindications, and irrespective of baseline LDL-cholesterol levels, “a moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus”. Moderate intensity statin therapy is defined as a daily dose that will lower LDL-cholesterol by an average of 30% to 50% of baseline level (3).

3.4 Eligibility criteria

Patients' charts were selected based on the following inclusion criteria:

- 1- Age between 40 to 75 years in year 2019.

2- T2dm diagnosis is listed in the Cerner® system ¹

3- Patient had a minimum of one visit to PHCC in which T2dm was the primary diagnosis during year 2019.

¹ SNOMED CT diagnostic codes were used to identify diagnosis of T2dm or T2dm with complications to accommodate for all possible T2dm diagnoses (95) (Appendix 2).

3.5 Exclusion criteria

Exclusion criteria are based on either statin prescription for indications other than primary prevention of ASCVD or any potential medical condition that would either temporarily or permanently contraindicate statin use, thus rendering the patient not eligible to receive statins. Exclusion diagnosis, identified by SNOMED CT diagnostic codes, were used to identify diagnosis of exclusion documented on the Cerner® system during the screening period (95) (Appendix 3).

- 1 Absolute contraindication to statin therapy (pregnancy, breastfeeding, liver disease or statin allergy)
- 2 Overt diagnosis of ASCVD (defined as diagnosis of angina, ACS, MI, any revascularization procedure, peripheral vascular disease, transient ischemic attacks, stroke, or any combination of the above) documented on the Cerner®
- 3 Familial hypercholesterolemia listed on system or elevation of LDL cholesterol above 190 mg/dl (27)
- 4 Patients with other types of diabetes (e.g., T1dm or gestational diabetes) recorded on the system

3.6 Variables and values

The following were extracted electronically for all patients fitting inclusion criteria:

- The main outcome was any prescription of statins recorded in the system during the calendar year 2019. The following statin agents were available in the PHCC formulary: Atorvastatin, Rosuvastatin, Simvastatin, Pravastatin, and Fluvastatin. Coded as a binary variable yes or no.
- Basic demographic characteristics: sex of the patient (male or female), nationality of the patient (Qatari or non-Qatari), all coded as binary variables.
- Age of patient in years
- Body mass index (BMI) in kg/m^2
- Last A1c records in year 2019
- Smoking status as recorded on the Cerner: non-smoker, former smoker, current smoker.
- Duration of the disease in years since first diagnosis of diabetes, as recorded manually by healthcare professional on the Cerner®
- Duration of system record since diabetes was recorded on the Cerner. System automatically counts from first entry of diabetes diagnosis in years.
- Diagnosis of hypertension, coded as a binary variable yes or no.
- Diagnosis of neuropathy, coded as a binary variable yes or no.
- Prescription of other non-statin lipid lowering drugs namely Fenofibrate, Gemfibrozil, Ezetimibe, or ω -3 fatty acid esters, coded as a binary variable yes or no.

- Prescription of anti-platelet medications, coded as a binary variable yes or no
- PHCC health centre in which the patient is registered.
- Exclusion diagnosis for excluded patients.
- Number of diabetes related visits in year 2019, where T2dm was the primary diagnosis.

The following variables were manually extracted from master lists

- Type of diabetes treatment: coded as oral, injectable, both, none.
- Number of daily injections of injectable diabetes medications. Injectable medications included insulins and/or injectable forms of glucagon like peptide-1 agonists extracted manually from excel sheet utilizing dosage scheme
- Number of daily tablets taken by patient for non-communicable diseases (NCD) medications only, extracted manually from excel sheet utilizing dosage scheme, not including multivitamins or other long-term non-NCD medications

3.7 Data collection, handling, and security

The Cerner® system fully replaced paper-form patient records and was rolled out in Qatar in 2014. The Cerner® was the only source of data. Data was extracted electronically by the help of Health and Information Management Department (HIM). For the purpose of this study, the HIM department provided an encoded anonymous excel list of eligible PHCC registered T2dm patients, as per above, together with their medications. Data were further cleaned, recoded, and saved on a disc with encrypted password with a cloud backup.

3.8 Data synthesis, analysis, and reporting

Data were cleaned and filtered as described in Fig 1. All data were then copied into STATA/MP® version 16.0 statistical software. Analysis was done on complete cases only. Categorical variables were summarized as proportions, percentages, frequency counts. Continuous variables were reported as means \pm standard deviations or as medians and interquartile ranges (IQR), when variables were not normally distributed. Two-sample T test was used to test for mean differences between two means of continuous variables; 95% confidence interval for the difference was reported. Two-sample Wilcoxon rank-sum (Mann-Whitney) test was used to compare medians when variables were not normally distributed. One-sample test of proportion was used to test for binary predictors proportions while the two-sample test of proportions was used to test for equality of proportions between different patient groups. Cochran-Armitage was used to test for trend for ordinal predictors.

Univariate logistic regression was used to assess associations and generate crude odds ratios of statin prescription with individual covariates. Multivariable logistic regression model was used to estimate adjusted odds ratio for all covariates and control for confounding.

Multivariable logistic model was built using a purposeful selection technique of predictor variables by including variables with p value threshold of < 0.25 from univariate logistic regression. After running initial multivariable logistic model, variables with p values greater than 0.05 were further excluded except for clinically important variables reported in the medical literature. The model was further assessed and revised for potential confounding. To control for potential confounding effect of practice, health center code was entered in the model as a variable, since patients were

registered in different health centers, which might have differing patient and provider characteristics. Likelihood ratio test was used to compare models. Hosmer-Lemeshow test, goodness of fit (GOF) test and Receiver Operating Characteristics curve (ROC) were run to assess the final model goodness of fit. As the model was used for adjustment rather than for prediction, no further diagnostics were planned. Since complete case analysis was performed, to assess selection bias, multivariable logistic models for complete case and whole sample populations were fitted with all variables excluding missing variables.

To further assess for the robustness of the study findings, a planned sensitivity analysis was performed by restricting analysis to patients registered for > 2 years, or patients with > 2 visits. The criteria for the analysis are based on clinical experience, i.e. patients who had more than two clinic visits or have been followed for more than 2 years are expected to be prescribed statins.

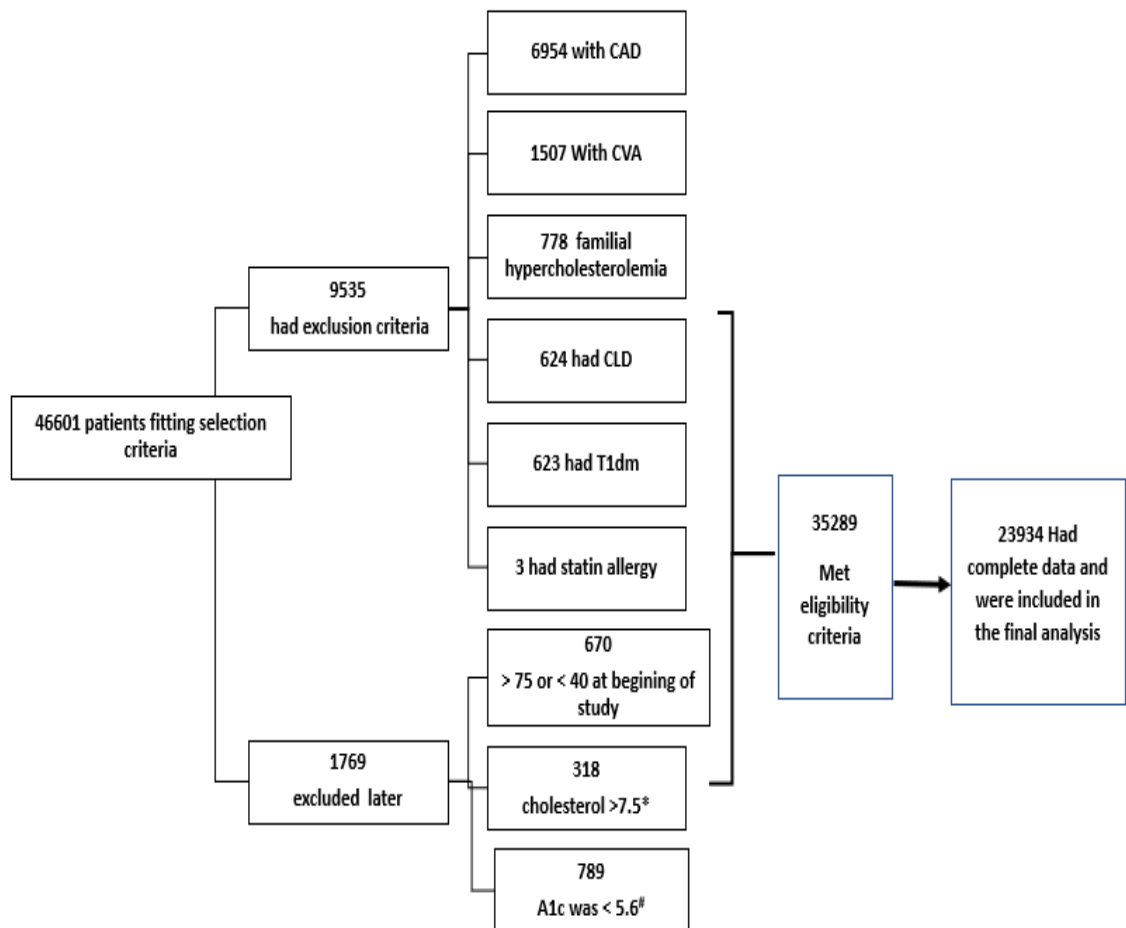
Reporting of the study followed Strengthening the Reporting of Observational studies in Epidemiology (STROBE) statement for reporting on cross-sectional studies (96).

3.9 Ethical compliance

The study protocol was approved by both PHCC (approval reference: PHCC/DCR/2019/12/041, Appendix 5) and Qatar University Institutional Review Boards (approval reference: QU-IRB 1524-E/21, Appendix 6). No patients' personal identifiers were collected. Patients' file numbers were numerically encoded by HIM. Since data were anonymous and collected electronically, no patient consent was obtained or needed.

CHAPTER FOUR: RESULTS

During 2019, out of 55,515 charts for registered patients with diabetes, 46,601 met the initial selection criteria (see methods); of which 11,304 charts had at least one exclusion criteria or had criteria that would otherwise be considered as exclusion, leaving 35,289 charts (whole sample population). Finally, 23,934 patients with complete data were included for analysis (see Figure 1).



*fits definition of familial hypercholesterolemia
would be considered nondiabetic

Figure 1: Study population

4.1 Study population characteristics

Of patients with complete case records (n=23,934), 57% were males and 31.9% were Qatari nationals. The mean age of the study population was 54.8 ± 8.25 years. The mean body mass index for the study population was 30.86 ± 6.1 kg/m². 77.8% (95% CI: 77.2-78.3) of the study population had no history of smoking, 22.2% (95% CI: 21.7-22.8) were either smokers or former smokers.

68.1% of the study population were hypertensive (95% CI: 67.5-68.7) while only 5.3% (95%CI 5.0-5.6%) of patients had associated diabetic neuropathy as a comorbidity. Median number of visits to GP clinics during the calendar year 2019 was 3 (min 1, max 27, IQR 1-4), 26.5 % of the patients had only one visit, 56% had 2 to 4 visits and 17.5% had 5 or more visits. Nearly 73 % of the study population were using oral agents only as treatment for their diabetes, 13.9% were using both oral and injectable agents, 1.7% of the patients were using injectable medications only, and 11% of patients had no documented treatment for diabetes in the system, suggesting they were on lifestyle modification. Patients were on a median of 4 NCD pills daily (min 0, Max 20, IQR 2-5). Patients receiving injectable medications were on a median of 1 injection daily (min 1, max 10, IQR 1-3). Only 7.2% (95% CI 6.8-7.5%) of the patients were prescribed a non-statin lipid lowering agent while 18.2% (95%CI 17.7-18.7%) were prescribed an anti-platelet agent.

Compared to females in the study, males were younger (mean difference -1.49 years 95%, CI: -1.28 - -1.7; P value < 0.000) and were considerably leaner (mean difference -3.93 kg/m², 95% CI: -3.79- -4.08, P value < 0.000). Males also had 35% higher prevalence of smoking but had 3% lower prevalence of associated diagnosis of hypertension (P value < 0.000) and 0.4% lower prevalence of associated diagnosis of

neuropathy (P value not significant (NS)). Additionally males had 0.3% lower prevalence of prescription of non-statin lipid lowering agents or antiplatelet medications (P value NS) and were receiving a median of one more pill and had a median of one more visit in year 2019 compared to females in the study (P value NS).

On the other hand, compared to Qatari patients in the study, non-Qatari patients were younger (mean difference -3.14 years 95%, CI: -2.92 - -3.36, P value < 0.000) and were considerably leaner (mean difference -2.91 kg/m², 95% CI: -3.07- -2.75, P value < 0.000). Non-Qatari patients also had 7% higher prevalence of smoking (P value <0.000) but had 1.5% lower prevalence of associated diagnosis of hypertension (P value 0.05) or neuropathy (P value <0.000). Additionally Non-Qatari patients had 2% lower prevalence of prescription of non-statin lipid lowering agents (P value <0.000) and 0.7 % lower prevalence of prescription antiplatelet medications (P value NS) but were similar in terms of numbers of daily pills, injections, or number of visits to GP clinic compared to Qatari patients in the study (P value NS).Table 1 summarizes complete case population characteristics.

Table 1: Complete Case Population Characteristics (n= 23,934)

Variable	Sub-variable	% or mean \pm SD	95% CI
Gender %	Male	57%	56.4-57.6%
	Female	43%	42.4-43.6%
Nationality %	Qatari	31.9%	31.4-32.5
	Non-Qatari	68.1%	67.5-68.6
Age years (mean \pm SD)	All	54.79 (8.25)	
	Male	54.15 (\pm 8.21)	
	Female	55.63 (\pm 8.23)**	
	Qatari	56.9 (\pm 8.16)	
	Non-Qatari	53.8 (\pm 8.10)**	
BMI (kg/m ²) (mean \pm SD)	All	30.86 (\pm 6.1)	
	Males	29.16 (\pm 5.13)	
	Females	33.10 (\pm 5.58)**	
	Qatari	32.83 (\pm 6.44)	
	Non-Qatari	29.93 (\pm 5.72)**	
Smoking %	Never	77.8%	77.2-78.3%
	Former	9.4%	9.0-9.7%
	Current	12.8%	12.4-13.3%
Smoking % (Male)	Never	63.0%	62.2-63.8%
	Former	15.8%	15.2-16.4%
	Current	21.2%	20.5-21.9%
Smoking % (Female)	Never	97.4%	97.0-97.8%
	Former	0.9%	0.7-1.1%
	Current	1.7%	1.5-1.9%
Smoking % (Qatari)	Never	82.9%	82.0-83.7%
	Former	5.4%	4.9-5.9%
	Current	11.7%	11.0-12.4%
Smoking % (Non-Qatari)	Never	75.4%	74.7-76.0%
	Former	11.2%	10.7-11.7%
	Current	13.4%	12.9-13.9%

Table 1(cont.):Complete Case Population Characteristics (n= 23,934)

Hypertension %	Yes	68.1%	67.5-68.7%
	Male	66.8%	66.0-67.6%
	Female	69.9% ^{**}	69.0-70.8%
	Qatari	69.2%	68.2-70.2%
	Non-Qatari	67.6% [#]	66.9-68.3%
Neuropathy %	Yes	5.3%	5.0-5.6%
	Male	5.1%	4.7-5.5%
	Female	5.5% ^{\$}	5.0-5.9%
	Qatari	6.4%	5.9-7.0%
	Non-Qatari	4.7% ^{**}	4.4-5.0%
Prescribed non-statin lipid drugs %	All	7.2%	6.8-7.5%
	Male	7.0%	6.6-7.5%
	Female	7.3% ^{\$}	6.8-7.8%
	Qatari	8.6%	8.0-9.2%
	Non-Qatari	6.5% ^{**}	6.1-6.9%
Prescribed anti-platelet %	All	18.2%	17.7-18.7%
	Male	18.1%	17.4-18.7%
	Female	18.4% ^{\$}	17.6-19.1%
	Qatari	18.0%	17.4-18.6%
	Non-Qatari	18.7% ^{\$}	17.8-19.6%
Treatment type %	None	10.7%	10.3-11.1%
	Oral only	73.7%	73.1-74.2%
	Injectable only	1.7%	1.5-1.9%
	Both oral and injectable	13.9%	13.5-14.3%
Patient's visits count %	1 visit only	26.55%	26.0-27.1%
	2-4 Visits	55.97%	55.33-56.60%
	5-7 visits	15.08%	14.63—15.54%
	≥8 visits	2.39%	2.20-2.59%

Table 1(cont.):Complete Case Population Characteristics (n= 23,934)

	Median	IQR	Min-Max
No. of tablets/day			
All	4	2-5	0-20
Male	4	2-5	0-11
Female	3	2-5 ^{\$}	0-11
Qatari	4	2-5	0-12
Non-Qatari	4	2-5 ^{\$}	0-11
No. of injections/day*			
All	1	1-3	1- 10
Male	1	1-2	1-6
Female	1	1-3 ^{\$}	1-6
Qatari	1	1-3	1-6
Non-Qatari	1	1-2 ^{\$}	1-6
Visit count in 2019			
All	3	1-4	1- 27
Male	3	1-4	1-27
Female	2	1-4 ^{\$}	1-25
Qatari	3	1-4	1- 27
Non-Qatari	3	1-4 ^{\$}	1- 18

BMI, Body Mass Index. CI, Confidence Interval. SD, Standard Deviation. IQR, Interquartile Range

* n =3,729, **P value for difference by group (i.e. males vs females or Qatari vs non-Qatari) < 0.000, #P for difference by group <0.05, \$ P for difference by group not significant

Both whole sample population (n=35,289) and complete case population (n=23,934) were nearly similar in terms of age, but were statistically significantly different in other basic demographics ($p<.05$). The whole sample population had 2% more males, 3% less Qatari people and 3% less diagnosis of hypertension among patients compared to complete case population. Table 2 summarizes the population characteristics for the whole sample population.

Table 2: Whole Sample Population Characteristics (n = 35,289)

Variable	Sub-variable	% or mean \pm SD	95% CI
Gender %	Male	58.9%	58.4-59.4
	Female	41.1%	40.5-41.5
Age years (mean \pm SD)	All	54.45 (\pm 8.33)	
	Male	53.83 (\pm 8.23)	
	Female	55.34 (\pm 8.38)**	
	Qatari	56.9 (\pm 8.3)	
	Non-Qatari	53.5 (\pm 8.1)**	
Nationality %	Qatari	28.7%	28.1-29.2
	Non-Qatari	71.3%	70.9-71.8
BMI (kg/m ²) (mean \pm SD) (n=28,505)	All	30.83 (\pm 6.13)	
	Males	29.13 (\pm 5.12)	
	Females	33.04 (\pm 6.6)**	
	Qatari	32.84 (\pm 6.44)	
	Non-Qatari	29.92 (\pm 5.72)**	
Smoking %	Never	60.9%	60.4-61.4
	Former	7.2%	6.9-7.5
	Current	10.6%	10.3-10.9
	Unknown	21.3%	20.8-21.7
Hypertension %	Yes	65.4%	64.9-65.9
	No	34.6%	34.1-35.1
	Male	63.8%	63.1-64.5
	Female	67.7% [^]	67.0-68.5
	Qatari	67.7%	66.8-68.6
	Non-Qatari	64.5% [^]	63.9-65.1
Neuropathy %	Yes	4.6%	4.3-7.8
	No	95.4%	95.2-95.7

Table 2 (cont.): Whole Sample Population Characteristics (n = 35,289)

Prescribed other lipid modifying drugs	Yes	6.6%	6.4-6.9
	No	93.4%	93.1-93.6
Prescribed anti-platelet	Yes	18.2%	17.8-18.6
	No	81.8%	81.4-82.2
Treatment type	None	10.9%	10.6-11.2
	Oral only	73.7%	73.3-74.2
	Injectable only	1.5%	1.4-1.6
	Both oral and injectable	13.9%	13.5-14.3
Patient's visits count	1 visit only	30.6%	30.1-31
	2-4 Visits	54.3%	53.7-54.8
	5-7 visits	13.2%	12.8-13.5
	≥8 visits	1.9%	1.8-2.0
	Median	IQR	Min-Max
No. of tablets/day	4	2-5	0-25
No. of injections/day *	1	1-2	0 - 10
Visit count in 2019	2	1-4	1 – 27

BMI, Body Mass Index. CI, Confidence Interval. SD, Standard Deviation. IQR, Interquartile Range

*n = 5,435, **P value for difference by group < 0.000.

There were 11,355 charts with missing information about two variables, smoking status, which was missing in 7,499 charts (21.3%), and/or BMI record which was missing in 6,784 charts (19.2%). Missingness in smoking was statistically associated with Qatari, but not patient's gender. BMI missingness showed no relation to either gender or nationality. The excluded patient charts were younger by an average of one year, had 6% more males, 10% less Qatari and 8% less diagnosis of hypertension compared to the complete case population. Table 3 summarizes the comparison between the complete cases and the excluded population

Table 3: Comparison for Included and Excluded Populations

Variable		Included (n=23934)	95%CI	Excluded (n=11355)	95%CI	Diff	CI for diff
Statin %	Yes	66.1%	65.5-66.7	53.15%	52.22-54.07	-13%*	-14.1 - -11.9
Gender	Male	57%	56.4-57.6	63.07%	62.18-63.96	6%*	4.9-7.1
Nationality	Qatari	31.9%	31.4-32.5	21.76%	21.00-22.53	-10.2%*	-9.2 - -11.2
Hypertension	Yes	68.1%	67.5-68.7	59.7%	58.8-60.6	-8.4%*	-9.5 - -7.3
Age years (mean \pm SD)	All	54.79 \pm 8.25		53.74 \pm 8.43		-1.05*	-0.86 - -1.24
	Male	54.15 \pm 8.21		53.23 \pm 8.23		-0.92	-0.68 - -1.16
	Female	55.63 \pm 8.23		54.62 \pm 8.70		-1.06*	-0.75- -1.37
	Qatari	56.9 \pm 8.16		56.71 \pm 8.83		-0.2*	-0.19- -0.59
	Non-Qatari	53.8 \pm 8.10		52.91 \pm 8.13		-0.9*	- 0.7- -1.1

CI, Confidence Interval. SD, Standard Deviation. Diff, Difference (value of excluded minus value of included). CI for Dif, Confidence Interval For Difference,

*P value for difference by group < 0.000

About 66 % (95% CI, 65.5-66.7%) of the patients were prescribed statins at least once during year 2019. Patients who were prescribed statins were older by a mean of 2.68 years ($P < 0.000$), slightly leaner (mean BMI difference -0.26 kg/m^2 , 95% CI: -0.12 - -0.45), had higher proportions of males and non-Qatari people and had higher prevalence rates of associated diagnosis of hypertension or neuropathy. Additionally they had higher prevalence of smoking, had higher prevalence of prescription of non-statin lipid lowering medications and had a median difference of one more visit and one more NCD pill compared to those not receiving statins ($P < 0.000$). Table 4 summarizes patient characteristics for those prescribed or not prescribed statins.

Table 4: Population Characteristics by Statin Prescription (n=23934)

Variable		<i>% Prescribed statin (n=15818)</i>	<i>95% CI</i>	<i>% Not prescribed statins (n=8116)</i>	<i>95% CI</i>	<i>P value for difference</i>
Age years	(mean ±SD)	55.7 (± 8.08)		53.02(± 8.30)		<0.000
BMI (kg/m ²)	(mean ±SD)	30.76 (±6.05)		31.05 (±6.23)		<0.000
Gender %	Male	59.3%	58.5-60.1%	52.5%	51.4-53.6%	<0.000
Nationality	Non-Qatari	69.4%	66.7-68.1%	65.4%	64.4-66.4%	<0.000
Smoking %	Never	76.4%	75.7-77.1%	80.6%	79.7-81.5%	<0.000
Hypertension %	Yes	74.9%	74.2-75.6%	55.0%	53.9-56.1%	<0.000
Neuropathy %	Yes	5.9%	5.5-6.3%	4%	3.6-4.4%	<0.000
Prescribed other lipid modifying drugs	Yes	8.2%	7.8-8.8%	5.0%	4.5-5.5%	<0.000
Prescribed anti-platelet	Yes	18%	17.4-18.6%	18.6%	17.8-19.4%	0.25
	Median	IQR		Median	IQR	
No. of tablets/day	4	6-3		3	1-4	0.000
No. of injections/day	1*	1-3*		1	1-2**	0.002**
Visit count in 2019	3	2-4		2	1-3	0.000

BMI, Body Mass Index. CI, Confidence Interval. SD, Standard Deviation. IQR, Interquartile Range. *n=3098 **n=631

Males and non-Qatari patients had about 6% and 3% higher rates of statin prescription compared to females and Qatari patients respectively ($P < 0.000$). Patients with reported history of smoking had higher rate of statin prescription compared to non-smoking patients. Former smokers had higher rate of statin prescription compared to either current smokers or non-smokers. An associated diagnosis of hypertension or neuropathy increased the rates of statin prescription by 20.5% and 8.7% respectively ($P < 0.000$). Statin prescription rate was 9% higher in patients co-prescribed other non-statin lipid lowering therapy ($P < 0.000$), but was 1% lower in patients co-prescribed an anti-platelet medication, although the latter was not statistically significant ($P = 0.21$) (Table 5).

Table 5: Statin Prescription by Patient Characteristics (n=23,934)

Variable	% prescribed statin	95% CI	P for difference
Prescribed statin	66.1%	65.5-66.7%	
Gender			
Male (n=13644)	68.8%	68.0-69.5%	<0.000
Female (n=10290)	62.5%	61.6-63.5%	
Nationality			
Qatari (n=7645)	63.3%	62.2-64.4%	<0.000
Non-Qatari (n=16289)	67.3%	66.7-68.1%	
Hypertension			
Yes (n=16309)	72.6%	71.9-73.3%	<0.000
No (n=7625)	52.1%	50.9-53.2%	
Neuropathy			
Yes (n=1258)	74.3%	71.8-76.7%	<0.000
No (n=22676)	65.6%	65.0-66.3%	
Smoking status*			
Nonsmoker (n=18615)	64.9%	64.2-65.5%	
Former smoker (n=2243)	73.6%	71.7-75.4%	
Current smoker (n=3076)	67.9%	66.3-69.6%	
Anti-platelet use			
Yes (n=4360)	65.3%	63.8-66.7 %	0.21
No (n= 19574)	66.3%	65.6-66.9 %	
Other lipid mediations use			
Yes (n=1713)	76.2%	74.1-78.2%	<0.000
No (n=22221)	65.3%	64.7-65.9%	

BMI, Body Mass Index. CI, Confidence Interval. SD, Standard Deviation. IQR, Interquartile Range.

Non-Qatari men had the highest rate of statin prescription while non-Qatari females had the lowest rates. The rate of statin prescription for Qatari men was slightly higher than Qatari females (P value 0.37) and both were higher than rates of non-Qatari females (p value 0.18). Results are shown in Table 6 and graphically displayed in Figure 2.

Table 6: Statin Prescription by Gender And Nationality (n=23,934)

Patient subgroup	Number of patients	Proportion receiving statin	95% CI
Non-Qatari female	5677	62.20%	60.9-63.5%
Qatari female	4613	62.90%	61.5-64.3%
Qatari male	3032	63.90%	62.2-65.6%
Non-Qatari male	10612	70.10%	69.2-71.0%

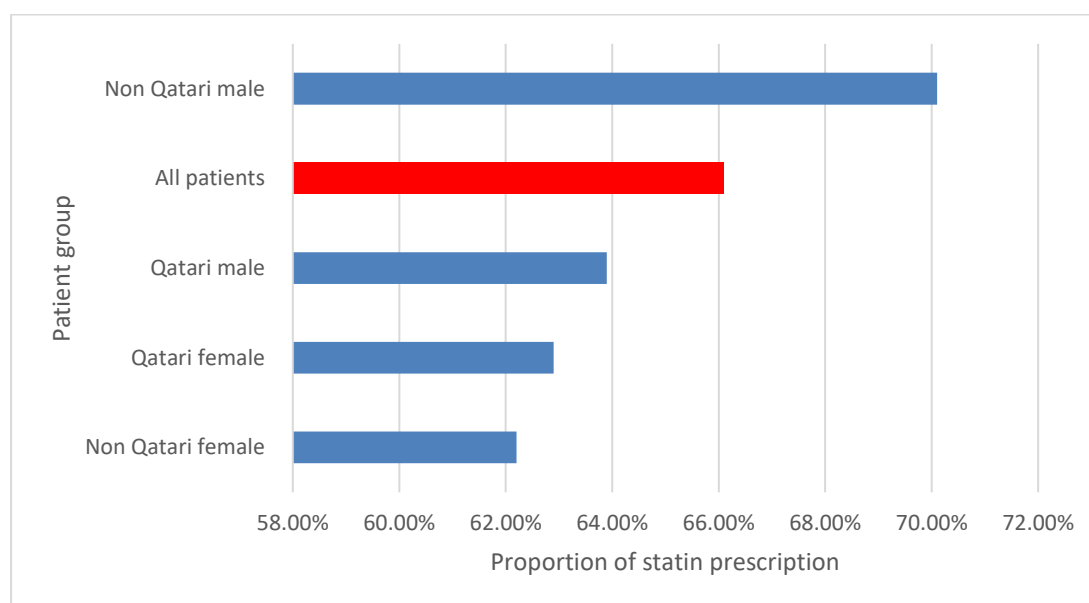


Figure 2 : Statin prescription by gender and nationality

4.2 Factors associated with statin prescription

In univariate analysis, statin prescription was positively associated with all predictors except for being Qatari, use of anti-platelet medications, or higher BMI. Having hypertension was the strongest predictor of statin prescription (odds ratio (OR) 2.44 [95% CI:2.30-2.58]) followed by being prescribed non-statin lipid lowering treatment (OR 1.70 [95% CI:1.51-1.90]), increased number of daily medication injections (OR 1.57/injection [95% CI:1.5-1.64]), history of smoking (i.e. former smoker (OR 1.51 [95% CI: 1.37-1.67]), current smoker (OR 1.15 [95% CI: 1.06-1.24]), having neuropathy (OR 1.52, [95% CI:1.33-1.72]), increasing daily pill number (OR 1.35/pill [95% CI: 1.33-1.37]), frequent visits to GP clinic (OR 1.36/visit [95% CI:1.34-1.38]), being a male (OR 1.32 [95% CI:1.25-1.39]), and increasing age (OR 1.041/year [95% CI:1.037-1.045]). There was a clear positive trend of increasing statin prescription with an increase in the number of visits to GP clinic ($p < 0.000$). On the other hand, statin prescription was negatively associated with being a Qatari (OR 0.84 [95% CI: 0.79-0.89]), increase in BMI (OR 0.992 [95% CI: 0.988-0.996) and being prescribed anti-platelet medication (OR 0.96[95% CI: 0.89-1.03]). Results of univariate logistic regression analysis are displayed in Table 7.

Table 7: Results of Univariate Logistic Regression Analysis (n=23,934)

Variable	Definition	OR	95% CI	P value
Gender	Female	Ref		
	male	1.32	1.25-1.39	<0.000
Nationality	Non-Qatari	Ref		
	Qatari	0.84	0.79-0.89	<0.000
Smoking status**	Never	ref		
	Former	1.51	1.37-1.67	<0.000
	Current	1.15	1.06-1.24	0.001
Hypertension	No	Ref		
	Yes	2.44	2.30-2.58	<0.000
Neuropathy	No	Ref		
	Yes	1.52	1.33-1.72	<0.000
Use of non-statin lipid lowering agent	No	Ref		
	Yes	1.70	1.51-1.90	<0.000
Use of anti-platelet	No	Ref		
	Yes	0.96	0.89-1.02	0.21
Injection count	per 1	1.57	1.50-1.64	<0.000
Tablet count	Per 1	1.35	1.33-1.37	<0.000
Age	per year > 40	1.041	1.037-1.045	<0.000
Visits	Per 1	1.36	1.34-1.38	<0.000
BMI	Per 1	0.992	0.988-0.996	<0.000
Visit number**	1	Ref		
	2 to 4	2.65	2.49-2.82	<0.000
	5 to 7	4.55	4.14-5.01	<0.000
	> 8	5.13	4.12-6.40	<0.000
Diabetes treatment type	None	Ref		
	Oral only	0.99	0.91-1.08	0.92
	Injectable only	0.97	0.88-1.08	0.88
	Both	0.97	0.87-1.09	0.67

BMI, Body mass index. 95%CI, 95% Confidence interval. OR, Odds ratio,
 **P for trend < 0.000, P for equal odds between variable subgroups <0.000.

The final multivariable model had 12 clinically important and/or statistically significant predictor variables and despite the Hosmer-Lemeshow test suggesting lack of fit, the model correctly classified 72.9% of the cases with an area under Receiver Operating Characteristics curve of 0.7465.

After controlling for other covariates in the model, statin prescription was positively associated with being a male (adjusted OR (aOR) 1.2 [95% CI: 1.12-1.28]), history of smoking (i.e. former smoker (aOR 1.16 [95% CI: 1.03-1.29]), current smoker (aOR 1.11 [95% CI: 1.01-1.21]), hypertension (aOR 1.51 [95% CI: 1.41-1.61]), being prescribed other non-statin lipid lowering medications (aOR 1.44 [95% CI: 1.27-1.63]), increasing age (aOR 1.03/year [95% CI: 1.026-1.034]), increasing daily pill number (aOR 1.23/pill [95% CI: 1.21-1.25]), increasing the number of daily medication injections (aOR 1.29/injection [95% CI: 1.23-1.35]), and frequent visits to GP clinic (aOR 1.22/visit [95% CI: 1.19-1.24]). Statin prescription was negatively associated with having a history of diabetic neuropathy (aOR 0.87 [95% CI: 0.75-1.0]), increasing BMI (aOR 0.996/unit [95% CI: 0.9892-1.00]), being Qatari (aOR 0.87 [95% CI: 0.81-0.93]) or being prescribed anti-platelet medication (aOR 0.96/unit [95% CI: 0.89-1.03]) although the later was not statistically significant. Results of multivariable logistic regression analysis are shown in Table 8.

Table 8: Results of Multivariable Logistic Regression Model Analysis (n=23,934)

Variable	Definition	aOR	95% CI	P value
Gender	Female	Ref		
	male	1.20	1.12-1.28	<0.000
Nationality	Non-Qatari	Ref		
	Qatari	0.87	0.81-93	<0.000
Smoking status	Never	Ref		
	Former	1.16	1.03-1.29	0.009
	Current	1.11	1.01-1.21	0.031
Hypertension	No	Ref		
	Yes	1.51	1.41-1.61	<0.000
Neuropathy	No	Ref		
	Yes	0.87	0.75-1.00	0.061
Use of non-statin lipid lowering agent	No	Ref		
	Yes	1.44	1.27-1.63	<0.000
Use of anti-platelet	No	Ref		
	Yes	0.97	0.89-1.04	0.346
Injection count	per 1	1.29	1.23-1.35	<0.000
Tablet count	Per 1	1.23	1.21-1.25	<0.000
Age	per year > 40	1.030	1.026-1.034	<0.000
Visits	Per 1	1.22	1.20-1.24	<0.000
BMI	Per 1	0.997	0.992-1.002	0.232

BMI, Body mass index. 95%CI, 95% Confidence interval., aOR: Adjusted odds ratio Adjusted for other covariates in the model (gender, nationality, smoking status, hypertension, neuropathy, use of other lipid medications, anti-platelet, injection count, tablet count, age, visits count, and patients BMI and practice location).

4.3 Sensitivity analysis

Sensitivity analysis confirmed robustness of our findings as direction of association between statin prescription and other covariates was not changed after restricting analysis to patients followed for > 2 years, or patients with > 2 visits as shown in Table 9, or when we restricted the analysis to either females only or Qatari patients only as shown in Table 10.

Table 9: Results of Multivariable Logistic Regression Model for Sensitivity Analysis Conditioned on Number of Visit and Years of Record

Variable	Definition	aOR* ^{\$} (n=17579)	95% CI	P value	aOR* ^{\$\$} (n=12099)	95% CI	P value
Gender	Female	Ref					
	male	1.01	1.001-1.21	0.046	1.19	1.09-1.29	<0.000
Nationality	Non-Qatari	Ref					
	Qatari	0.79	0.71-0.86	<0.000	0.90	0.82-0.98	0.018
Smoking status	Never	ref					
	Former	1.23	1.05-1.42	0.007	1.16	1.01-1.32	0.036
	Current	1.21	1.06-1.38	0.004	1.14	1.02-1.27	0.022
Hypertension	No	Ref					
	Yes	1.50	1.36-1.64	<0.000	1.54	1.42-1.66	<0.000
Neuropathy	No	Ref					
	Yes	0.87	0.73-1.03	0.107	0.86	0.72-1.01	0.068
Use of non-statin lipid lowering agent	No	Ref					
	Yes	1.19	1.01-1.39	0.032	1.27	1.10-1.45	0.001
Use of anti-platelet	No	Ref					
	Yes	0.98	0.88-1.09	0.77	0.98	0.89-1.08	0.769
Injection count	per 1	1.27	1.20-1.34	<0.000	1.27	1.20-1.33	<0.000
Tablet count	Per 1	1.21	1.19-1.23	<0.000	1.15	1.13-1.17	<0.000
Age	per year > 40	1.022	1.017-1.027	<0.000	1.032	1.027-1.037	<0.000
Visits	Per visit	1.19	1.16-1.21	<0.000	1.13	1.10-1.16	<0.000
BMI	Per 1kg/m ²	0.996	0.989-1.003	0.267	0.996	0.990-1.001	0.177

BMI, Body mass index. 95%CI, 95% Confidence interval. aOR, Adjusted odds ratio

^{\$} conditioned on > 2 visits.

^{\$\$} conditioned on > 2 record years.

*Adjusted for other covariates in the model (gender, nationality, smoking status, hypertension, neuropathy, use of other lipid medications, anti-platelet, injection count, tablet count, age, visits count, and patients BMI and practice location).

Table 10: Results of Multivariable Logistic Regression Model Analysis for Female and Qatari Subgroups

Variable	Definition	Study population (n= 23,934)		Female only (n=10,248)		Qatari only (n= 7,639)	
		aOR#	95% CI	aOR#	95% CI	aOR#	95% CI
Gender	Female	Ref				Ref	
	male	1.20	1.12-1.28	Omitted		0.97*	0.85-1.10
Nationality	Non-Qatari	Ref		Ref			
	Qatari	0.87	0.81-93	0.96*	0.86-1.06	Omitted	
Smoking status	Never	Ref		Ref		Ref	
	Former	1.16	1.03-1.29	1.03*	0.64-1.66	1.06*	0.82-1.37
	Current	1.11	1.01-1.21	1.27*	0.89-1.81	1.01*	0.84-1.21
Hypertension	No	Ref		Ref		Ref	
	Yes	1.51	1.41-1.61	1.63	1.47-1.80	1.55	1.37-1.74
Neuropathy	No	Ref		Ref		Ref	
	Yes	0.87	0.75-1.00	0.99*	0.79-1.2	0.89	0.69-1.10
Use of non-statin lipid lowering agent	No	Ref		Ref		Ref	
	Yes	1.44	1.27-1.63	1.63	1.34-1.97	1.65	1.33-2.03
Use of anti-platelet	No	Ref		Ref		Ref	
	Yes	0.97*	0.89-1.04	0.95*	0.84-1.06	0.96*	0.83-1.10
Injection count	per 1	1.29	1.23-1.35	1.29	1.20-1.37	1.25	1.15-1.34
Tablet count	Per 1	1.23	1.21-1.25	1.25	1.22-1.28	1.30	1.27-1.33

Table 10 (cont.): Results of Multivariable Logistic Regression Model Analysis for Female and Qatari Subgroups

Age	per year > 40	1.030	1.026-1.034	1.049	1.043-1.055	1.035	1.028-1.042
Visits	Per visit	1.22	1.20-1.24	1.21	1.17-1.25	1.17	1.13-1.21
BMI	Per unit	0.997*	0.992-1.002	0.989	0.982-0.996	0.992*	0.983-1.001

BMI, Body mass index. 95%CI, 95% Confidence interval. aOR, Adjusted odds ratio

Adjusted for other covariates in the model (gender, nationality, smoking status, hypertension, neuropathy, use of other lipid medications, anti-platelet, injection count, tablet count, age, visits count, and patients BMI and practice location).

*P value not significant > 0.05

Because of the difference in population characteristics between complete-case and the whole sample populations, another multivariable logistic model was fitted with all predictors excluding missing variables of smoking status and BMI to assess the assumption that some of the predictors might have behaved differently between the two populations. The model was run for both complete-case and the whole population. All predictors produced similar results in terms of the direction of the associations, but with slightly different magnitudes, except for co-prescription of anti-platelets which showed a reverse direction in the whole sample population (Table 11). This might be due to the potential confounding effect of the excluded variables or possible interaction between other covariates in the model. Overall, the small difference in the results between the two populations suggested that exclusion of incomplete patient charts had little effect on the final model results.

Table 11: Comparison Results of Multivariable Logistic Regression Model Analysis for Complete Case vs Whole Sample Populations after

Excluding Missing Variables

Variable	Definition	aOR* (n=23934)	95% CI	P value	aOR* (n=35289)	95% CI	P value
Gender	Female	Ref					
	male	1.26	1.18-1.34	<0.000	1.27	1.21-1.33	<0.000
Nationality	Non-Qatari	Ref					
	Qatari	0.87	0.81-0.93	<0.000	0.96	0.90-1.01	0.120
Hypertension	No	Ref					
	Yes	1.50	1.40-1.50	<0.000	1.6	1.52-1.69	<0.000
Neuropathy	No	Ref					
	Yes	0.87	0.75-1.01	0.064	0.93	0.81-1.05	0.240
Use of non-statin lipid lowering agent	No	Ref					
	Yes	1.44	1.27-1.63	<0.000	1.59	1.43-1.76	<0.000
Use of anti-platelet	No	Ref					
	Yes	0.96	0.89-1.04	0.349	1.02	0.96-1.08	0.552
Injection count	per 1	1.29	1.23-1.35	<0.000	1.30	1.25-1.35	<0.000
Tablet count	Per 1	1.23	1.21-1.25	<0.000	1.23	1.21-1.25	<0.000
Age	per year > 40	1.029	1.025-1.033	<0.000	1.026	1.023-1.029	<0.000
Visits	Per 1	1.22	1.20-1.24	<0.000	1.25	1.23-1.27	<0.000

95%CI, 95% Confidence interval. aOR, Adjusted odds ratio

*Adjusted for other covariates in the model (gender, nationality, hypertension, neuropathy, use of other lipid medications, anti-platelet, injection count, tablet count, age, visits count, patients age and practice location).

Because females and Qatari patients had 35% and 7% lower prevalence of smoking compared to males and non-Qatari patients respectively, and to explore potential effect of smoking on difference in statin prescription, we further analyzed nonsmoking population. Of the nonsmoking population (n=18,615), 53.8% were females, 65.9% were non-Qatari. Males and non-Qatari patients were younger by a mean of 1.4 years and 3.3 years and were leaner by a mean of 4kg/m² and 3 4kg/m² compared to females and Qatari patients, respectively (P value <0.000). Additionally males and non-Qatari patients had 2% and 1.8% lower prevalence of hypertension and 1% and 2% lower prevalence of prescription of non-statin lipid lowering medications compared to females and Qatari patients, respectively (P value <0.000). Rest of patients characteristics were not statistically different.

Overall statin prescription rate was 67.7%, females and Qatari patients had about 5% and 2% lower statin prescription rates compared to males and non-Qatari patients (62.5% vs 67.7% and 63.2% vs 65.7% respectively, P value <0.000) with virtually no change in results of multivariate logistic model when we restricted analysis to nonsmoking patients only. Table 12 summarizes analysis findings for nonsmoking patients.

Table 12: Results of Multivariable Logistic Regression Model Analysis for Nonsmoking Patients (n=18615)

Variable	Definition	aOR	95% CI	P value
Gender	Female	Ref		
	male	1.21	1.12-1.30	<0.000
Nationality	Non-Qatari	Ref		
	Qatari	0.93	0.86-1.00	0.062
Hypertension	No	Ref		
	Yes	1.51	1.40-1.62	<0.000
Neuropathy	No	Ref		
	Yes	0.89	0.75-1.04	0.159
Use of non-statin lipid lowering agent	No	Ref		
	Yes	1.43	1.24-1.65	<0.000
Use of anti-platelet	No	Ref		
	Yes	0.93	0.86-1.01	0.121
Injection count	per 1	1.28	1.22-1.35	<0.000
Tablet count	Per 1	1.23	1.21-1.25	<0.000
Age	per year > 40	1.032	1.028-1.037	<0.000
Visits	Per 1	1.22	1.19-1.24	<0.000
BMI	Per 1	0.995	0.989-1.000	0.08

BMI, Body mass index. 95%CI, 95% Confidence interval., aOR: Adjusted odds ratio Adjusted for other covariates in the model (gender, nationality, hypertension, neuropathy, use of other lipid medications, anti-platelet, injection count, tablet count, age, visits count, and patients BMI and practice location).

To further explore potential reasons for the lower odds associated with Qatari nationality, female gender, and higher BMI, the study logistic model was examined for the presence of potential interaction of the above variables with each other and with other covariates in the model after centering the model at mean BMI of the sample. Significant positive 1st order interaction was found between being a male and higher BMI. On the other hand, significant negative 1st order interaction was found between being male and diagnosis of hypertension or being Qatari. Results are summarized in Table 13.

Table 13: Results of Multivariable Logistic Regression Model Analysis Including Interactions (n=23934)

Variable	Definition	aOR*	95% CI	P value
Gender	Female	Ref		
	male	1.63	1.45-1.82	<0.000
Nationality	Non-Qatari	Ref		
	Qatari	1.04	0.95-1.14	0.382
Smoking status**	Never	Ref		
	Former	1.16	1.04-1.30	0.008
	Current	1.12	1.02-1.23	0.018
Hypertension	No	Ref		
	Yes	1.79	1.62-1.97	<0.000
Neuropathy	No	Ref		
	Yes	0.87	0.75-1.00	0.067
Use of non-statin lipid lowering agent	No	Ref		
	Yes	1.43	1.26-1.62	<0.000
Use of anti-platelet	No	Ref		
	Yes	0.97	0.90-1.04	0.375
Injection count	per 1	1.29	1.23-1.35	<0.000
Tablet count	Per 1	1.24	1.22-1.26	<0.000
Age	per year > 40	1.030	1.026-1.034	<0.000
Visits	Per 1	1.22	1.19-1.25	<0.000
BMIc	Per 1	0.989	0.982-0.996	0.002
Gender#Nationality	Male #Qatari	0.69	0.60-0.79	<0.000

Table 13 (cont.): Results of Multivariable Logistic Regression Model Analysis Including Interactions (n=23934)

Gender#Hypertension	Male #Yes	0.74	0.65-0.83	<0.000
Gender#c.BMlc	Male	1.017	1.006-1.027	0.002

BMlc, Body mass index centered at the mean of the sample. 95%CI, 95% Confidence interval. aOR, Adjusted odds ratio

*Adjusted for other covariates in the model (gender, nationality, hypertension, neuropathy, smoking status, BMlc, use of other lipid medications, anti-platelet, injection count, tablet count, age, visits count, patients age and practice location).

Stratified analysis of the interaction model showed that hypertensive non-Qatari males had the highest odds for statin prescription (aOR 2.19 [95%CI 1.96-2.44]). The odds of statin prescription for both normotensive and hypertensive Qatari male (aOR 1.20 [95%CI 1.05-1.35] and aOR 1.58 [95%CI 1.39-1.80] respectively) were much lower than either normotensive non-Qatari males (aOR 1.66 [95% CI 1.48-1.86]) or hypertensive non-Qatari females (aOR 1.66 [95% CI 1.48-1.86]). Results of stratified analysis are summarized in Table 14.

Table 14: Results of Multivariable Logistic Regression Model Stratified Analysis Summary (n=23934)

Patient covariate combination	aOR*	95%CI	P value
Normotensive Non-Qatari female	Ref		
Normotensive Qatari female	1.04	0.95-1.13	0.382
Normotensive Qatari male	1.20	1.05-1.35	0.008
Hypertensive Qatari male	1.58	1.39-1.80	<0.000
Normotensive Non-Qatari male	1.66	1.48-1.86	<0.000
Hypertensive Non-Qatari female	1.79	1.62-1.97	<0.000
Hypertensive Qatari female	1.87	1.63-2.14	<0.000
Hypertensive Non-Qatari male	2.19	1.96-2.44	<0.000

95%CI: 95% Confidence interval., aOR: Adjusted odds ratio

*Adjusted for other covariates in the model (neuropathy, smoking status, use of other lipid medications, anti-platelet, injection count, tablet count, age, visits count, patients age and practice location).

CHAPTER FIVE: DISCUSSION

To the best of our knowledge, this is the first study to report on statin prescription in primary care settings in Qatar after the updated diabetes management guidelines. Three years after the guidelines were release, the rate of statin prescription for primary prevention of ASCVD among patients with type 2 diabetes in primary care settings was suboptimal. One out of three eligible patients was not receiving statins. This is despite the expected 60% increased eligibility for statins in the African and Middle Eastern countries after the updated ACC/AHA guideline publication (97). These rates are virtually no different than what was reported locally in 2013 in secondary care settings (32) and quite like what was reported in many countries across the globe. Researchers of the PINNACLE registry (Practice INNovation And CLinical Excellence) showed that there was only a 4% increase in the rate of prescription of statins to eligible patients 14 months after the publication of the AHA/ACC update in 2013 (98), and that 2 years after the 2013 AHA/ACC guidelines update, prescription rates of statins for primary prevention to patients with diabetes in primary care settings showed a modest increase in statins prescription (99).

The factors associated with higher odds of statin prescription in this study included increasing age, male sex, history of smoking, or hypertension. Similar results have been reported in other studies (74,76,79). Further, our results are consistent with the strong association between statin prescription for ASCVD prevention and advancing age or male sex (100). Hypertension and tobacco smoking were reported as a major determinant for institution of recommended guidelines for preventive drugs by physicians, especially if associated with diabetes (101), and thus would probably

invoke HCPs to prescribe or maintain use of statins in patients with such risk factors (31). The higher odds seen in former smoker compared to current smokers is probably due to that ex-smoker patients might be more health conscious and more accepting of additional ASCVD protective interventions.

Co-prescription of non-statin lipid lowering medication was similarly associated with increased odds of statin prescription in this study which was consistent with other studies reporting similar association (69,76). Guidelines recommend the use of non-statin lipid lowering medication when blood lipid targets are not achieved by maximally tolerated or maximally recommended statin dose (26,3). This could be explained by that patients who are prescribed non-statin lipid lowering drugs probably had their blood lipid profile checked more frequently and therefore had higher chances of detecting blood lipid abnormalities like high cholesterol levels. This would allow physicians to discuss and assess ASCVD risk and possibly increase the rate of use of lipid modifying drugs (31,101).

In this study, the increase in the number of daily NCD pills or daily medication injections was associated with higher odds of statin prescription. This might reflect disease complexity due to coexisting comorbidities, like hypertension or neuropathy, which usually necessitates additional treatments. Simultaneously, the increased number of comorbidities might induce both patient and physician to be more vigilant in ASCVD risk reduction. The high number of tablets and medication injections is consistent with findings in patients with T2dm in the UK who were prescribed 8.6 ± 3.9 tablets (max 22)/day, 2.6 ± 1.6 injections (max 7)/day, 97% of which were guideline-recommended (103).

Finally, the increased number of visits to GP clinics was also associated with higher odds of statin prescription. This is consistent with recent findings in other studies (104). A possible explanation is that patients who had more encounters with their physicians had higher chances of medication reconciliation or had more chances to discuss their concerns or preferences regarding statin treatment. This would probably increase the chance of being prescribed or maintained on statins.

On the other hand, our study has shown that being female, Qatari national, being prescribed anti-platelet medication, having diabetic neuropathy, or having higher BMI were all associated with lower odds of statin prescription.

Women and Qatari nationals are at higher risk for ASCVD incidence or mortality, as reported in literature (18,59,60), despite these observations, prevalence and odds of statin prescription were lower in both groups compared to males and non-Qatari patients, respectively. This might have been due to that the large proportion of non-Qatari males, which is more than 44% of the total patient population and is more than the whole Qatari or female population groups, had inflated the odds for both males and non-Qatari patient groups.

Another possible explanation is that the differences in patient characteristics between patient groups have led to this discrepancy in odds of statin prescription. However apart from marked difference in smoking history, which was higher in males and non-Qatari population groups, other characteristics were nearly similar. Furthermore our analysis has shown that this discrepancy in odds of statin prescription was unchanged when analysis was restricted to nonsmoking patients only, females only or Qatari patients only suggesting that being Qatari or female independently predict lower odds of being prescribed statins.

One more potential reason for the difference is that the positive effect modification of male gender on BMI nearly cancelled the negative effect higher BMI on odds of statin prescription in male population of this study. This could in part explain why females had lower odds of statin prescription especially given that females were more obese compared to males in this study. The negative effect modification of Qatari nationality on male gender and hypertension led to lower odds of statin prescription in Qatari males compared to non-Qatari males or hypertensive non-Qatari females and could be another driving factor for the Qatari population's lower odds of statin prescription.

The lower odds of statin prescription in females is consistent with findings in other countries (75,80). A recent meta-analysis of 43 studies with more than 2 million primary care patients reported that females were 10% less likely to get statins for primary prevention of ASCVD compared to men with similar cardiovascular risk (106). It confirms that the updated guidelines failed to close the gender and disparity gap in terms of statin prescription (99).

Our finding that the Qatari population has lower odds of statin prescription is against the notation that free medication increases the chances of being given statins in Qatar. However, affordability might still be an issue for some non-Qatari expats who copay 10-20% of medication costs which might, in part, explain why less than 66% of non-Qatari expats were on statins.

Moreover, unlike what was reported in the literature in the primary and secondary care settings (69,94), being prescribed anti-platelet medications decreased the odds of statin prescription by 4%, although the result was not statistically significant. A plausible explanation for lower odds in aspirin users is that some patients would rather not use

statins and prefer to use another preventive medication like aspirin, especially if they are worried about possible side effects of statin therapy (102).

Patients having diabetic neuropathy had 13% lower odds of statin prescription compared to patients without neuropathy. This is in contrast to other studies that linked statin prescription to the presence of diabetic complications, more specifically to the presence of nephropathy (77). This could be due to the unfounded claims that statins are a cause of peripheral neuropathy (105).

5.1 Conclusion and implication for future research

Statin prescription for the primary prevention of ASCVD in T2dm patients is suboptimal in primary care settings in Qatar. Patient attributes associated with statin prescription are mostly concordant with current literature. However, odds of statin prescription were lower in patients who are at higher risk of ASCVD like females and Qatari patients.

This study explored only one side of statin usage utilizing prescribing information. Still, it did not explore other important aspects of statin use like repeated prescription, patient adherence to their statins, or attainment of specific lipid targets with treatment. All these aspects have been reported to be more important than mere statin prescription (54,107). Recent studies have demonstrated that neither prescription of statins per se nor updating clinical guidelines was enough to achieve proper risk reduction (92,107). In the USA, only 14 % of patients prescribed statins were at the lipid target at 12 months after the updated 2013 ACC/AHH guidelines on statins were released (108).

The low rates in this study should be addressed in the context of the complexity of the statin prescription process which involves the patient, physician, guidelines, and system

factors. Further studies exploring each of these aspects are needed to develop strategies to improve the prescription of statins.

Addressing patients' beliefs and behaviors such as patients' descent from taking statins or reluctance to maintain statin intake need to be studied as a potential source for low statin prescription rates in Qatar. It will be worthwhile at the same time to study physicians' awareness of the current guidelines together with assessments on their familiarity and agreement with its content.

Finally, exploring HCPs' opinions and perceptions on the adoptability and applicability of the current guidelines in primary care settings is paramount. Regional experts issued a consensus statement accepting universal use of statins in diabetic patients above 40 years of age (109). However, some experts still argue that western guidelines are neither tested nor adaptable to our societies given that dyslipidemia pictures in the Middle East and Asia are different from Western countries (110).

5.2 Strengths and Limitations

This is the first study, to the best of our knowledge, to report on statin prescription in Qatar's primary care settings. The large sample size and inclusion of all PHCC centers in Qatar with adequate control for confounding variables using multivariable analysis and inclusion of most of the variables associated with statin prescription reported in literature adds to the significance of our findings and enhances the generalizability of the study's findings to PHCC settings.

Still, the study has some limitations, and our results should be interpreted with caution. First, defining the outcome as any statin prescription rather than prescription of

moderate-intensity statin may have prevented assessing the level of physicians' adherence to the current guidelines regarding the choice of statin intensity, but at the same time allowed us to capture prescriptions of lower-intensity statins. This would be very helpful, especially when statin dose or type would have been changed to lower potency dose or agent if side effects of more potent statins were faced.

Second, the study included only patients registered to the PHCC and did not capture aspects of statin prescription in primary care settings in private sector. Thus, it has limited generalizability outside Qatar's PHCC T2dm population.

Third, the retrospective data collection had its known shortcomings including incompleteness and missingness. Additionally, the use of EMR as the main source of information does not come without limitations (111). Much of the data like duration of the disease, anthropometric measures, diagnosis of diabetic comorbidities and complications relied heavily on manual entry by HCPs. Failing to document any of the above, like for example ASCVD as a comorbidity might have misclassified some patients as primary prevention while having ASCVD and would slightly inflate the proportion of patients receiving statins as evidence suggests that statin prescription was higher in this group compared to primary prevention populations (108). The problem of poor documentation of other diabetic complications was a limitation to their inclusion in the study. We were unable to explore the association between statin prescription and other diabetic microvascular complications due to the fact that less than 1% had listed diagnosis of any diabetic eye disease or diabetic nephropathy, unlike diabetic neuropathy. A diagnosis of diabetic neuropathy needs to be on the patient's record to allow dispensing of specific drugs. Many patients with diabetic neuropathy would be prescribed medications like gabapentin or pregabalin to relieve their

neuropathic symptoms, both drugs are listed under the controlled drugs act in the state of Qatar. Other limitations to use of EMR could be due to the completeness of patients' medication reconciliation records by HCPs. If it were not done properly and in a timely manner, it would over or underestimate the number of daily pills or injections. It might also misclassify the study's outcome if patients obtained their statins from other sources, and it had not documented so on EMR.

Fourth, since the patients were registered to different practices that might have been different in terms of population and/or practitioner characteristics, a potential cluster effect based on the center where the patient was registered might have been present. To control for this potential practice effect based on the health center, we included the health center codes in all models. Additionally, we calculated the Intraclass Correlation Coefficients (ICC) for all predictors in the model using health center code as a second-level variable and found low ICC of 0.015-0.049. Based on this low ICC and due to time constraints, we did not perform cluster analysis of the data.

Lastly, we were unable to associate statin prescription to either glycemic control as judged by A1c level or to baseline lipid levels in the study for two reasons. The 1st is that the A1c and/or blood lipid levels were missing for many patients and the 2nd is due to the cross-sectional study design which limited our ability to determine whether the available A1c and lipid profile readings antedated statin prescription. Additionally we were unable to verify achievement of a target LDL-cholesterol, defined as reaching a specific LDL-cholesterol target level or a 50% reduction from baseline levels (3), in patients prescribed statins and for the same reasons. Future cohort design studies are better suited to overcome such limitations.

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APPENDICES

Appendix 1: Studies reporting on statin prescription

Country	Year	Population	age	Practice type	Prevention level	Rate of statin prescription	Factors associated with higher prescription rates of statins	Neutral factors	Guidance source	Ref
Malaysia	2015-16	T2dm	40-75	Secondary care	NR	81%	Lower BMI, shorter duration of diabetes	Age, gender, and ethnicity	2013 AHA/ACC	(68)
Malaysia	2016-17	T2dm	40-75	Primary care	Primary	87%	NR	NR	2013 AHA/ACC	(67)
India	2016	T2dm	<40-60+	Secondary specialist care	NR	55.2	Male sex, high CVD risk	NR	2013 AHA/ACC	(75)
UK	2016	T2dm without CKD	40-74	Mixed	Primary	66%	NR	NR	NICE 2014	(72)
Sweden	2014	T2dm	18+	Primary care	Primary	47%	Age, smoking, longer diabetes duration, on treatment for diabetes, Hypertension, Anti-platelet, female sex	NR	Swedish guidance	(76)
USA	2012-13	T2dm, men	40-75	Primary care	Primary and secondary	68%	Older, Hypertension, CAD, more visits, other lipid treatment		2013 AHA/ACC	(69)
USA	2015	T2dm	40-75	Mixed	Primary	67%	NR	NR	2013 AHA/ACC	(112)

Netherlands	2006-2012	T2dm	>18	Primary care	Primary	67%	Older, higher BMI	Gender HTN	Dutch Cardiovascular Risk Management guidelines	(71)
Scotland	2008	T1dm or T2dm	40-80	Primary care	Primary	68%	Higher BMI, age 50-65, higher T cholesterol and h/o smoking	Gender income	Scottish Intercollegiate Guidance Network (SIGN)	(70)
South Africa	2017-18	T2dm	18+	Secondary care	Mixed	45%	High LDL, chronic kidney disease, DM duration	Age, Gender, Hypertension BMI,CAD	2017 SEMDSA diabetes management guidelines	(77)
Turkey	2017	T2dm	18+	Tertiary care	Mixed	43%	NR	NR	Society of Endocrinology and Metabolism of Turkey 2017	(78)
Ethiopia	2018	T2dm	40-75	OPD	Primary	55%	NR	NR	2013 AHA/ACC	(74)
Germany	2009	T2dm	NR	OPD	Primary	18.5%	High CVD risk, Hypertension, smoking, high cholesterol			(79)
Kuwait	2013	T2dm	<75	Mixed	Primary	56%	NR	NR	Multiple	(73)

T2dm: Type 2 diabetes., NR: not reported, BMI: Body mass index, CKD: chronic kidney disease, CVD: cardiovascular disease,

*Appendix 2: List of SNOWMED diagnosis for T2dm***

Type 2 diabetes mellitus	Concept ID 44054006
- Diabetes mellitus type 2 in nonobese	Concept ID 359642000
Diabetes mellitus type 2 in obese	Concept ID 81531005
Insulin treated type 2 diabetes mellitus	Concept ID 237599002
Pre-existing type 2 diabetes mellitus	Concept ID: 199230006
Type II diabetes mellitus without complication - Type 2	Concept ID: 313436004
Polyneuropathy co-occurrent and due to type 2 diabetes mellitus OR Polyneuropathy due to type 2 diabetes mellitus	Concept ID: 713706002
Hyperglycemia due to type 2 diabetes mellitus -	Concept ID: 368051000119109
Type 2 diabetic on insulin	Concept ID: 24471000000103
Type 2 diabetic on diet only	Concept ID: 24481000000101
Chronic kidney disease due to type 2 diabetes mellitus	Concept ID: 771000119108
Brittle type 2 diabetes mellitus	Concept ID: 445353002

** from <https://snomedbrowser.com/>

*Appendix 3: List of SNOWMED exclusion diagnosis***

Diabetes mellitus type 1	Concept ID: 46635009
Peripheral circulatory disorder associated with diabetes mellitus-OR Peripheral circulatory disorder associated with diabetes mellitus	Concept ID: 421895002
Peripheral vascular disease	Concept ID: 400047006
Angina associated with type 2 diabetes mellitus -	Concept ID: 791000119109
Arteriosclerotic vascular disease	Concept ID: 72092001
- Atherosclerosis artery	Concept ID: 441574008
Cerebrovascular disease OR CVD - Cerebrovascular disease	Concept ID: 62914000
H/O: cerebrovascular disease -OR History of cerebrovascular disease	Concept ID: 308064009
History of placement of stent for coronary artery disease -	Concept ID: 428375006
Angina pectoris - OR Angina	Concept ID: 194828000
Myocardial infarction -OR MI -	Concept ID: 22298006
History of myocardial infarction -OR Past history of myocardial infarction	Concept ID: 399211009
Pregnant – OR Pregnancy confirmed	Concept ID: 77386006
Normal pregnancy -	Concept ID: 72892002
Lactation	Concept ID: 82374005
Chronic liver disease -	Concept ID: 328383001
Statin allergy -OR 3-Hydroxy-3-methylglutaryl-coenzyme A (HMG CoA)reductase inhibitor allergy	Concept ID: 294970008
Familial hypercholesterolemia – OR - Familial hyperbetalipoproteinemia OR - Essential familial hypercholesterolemia	Concept ID: 398036000
Primary hypercholesterolemia	Concept ID: 238076009

** from <https://snomedbrowser.com/>

Appendix 4: List of NCD medications available in PHCC formulary

Antihypertensive medication	Fosinopril Lisinopril lisinopril plus hydrochlorothiazide Perindopril Perindopril plus indapamide Perindopril plus amlodipine Ramipril Valsartan Valsartan plus Amlodipine Valsartan plus hydrochlorothiazide Irbesartan Irbesartan plus hydrochlorothiazide Amlodipine Nifedipine	felodipine Atenolol plus chlorthalidone Atenolol Carvedilol Bisoprolol Metoprolol Indapamide Chlorthalidone furosemide Moxinidine Alpha methyl dopa Clonidine
Oral diabetes	Metformin metformin plus vildagliptin metformin plus sitagliptin sitagliptin vildagliptin linagliptin Glibenclamide Glibenclamide plus metformin metformin	Gliclazide Glimepiride Pioglitazone Dapagliflozin Empagliflozin Empagliflozin plus metformin Dapagliflozin plus Acarbose Repaglinide
Injectable forms	Insulin aspart insulin lispro insulin glargine insulin degludec insulin aspart plus degludec insulin aspart plus aspart protamine	Insulin lispro plus lispro protamine Insulin degludec plus liraglutide premix insulin Dulaglutide Exenatide Liraglutide
Anti-platelet medications	Aspirin Clopidogrel	
Neuropathy	Carbamazepine Duloxetine Gabapentin	pregabalin Amitriptyline
Statin	Atorvastatin Rosuvastatin Pravastatin	Simvastatin Fluvastatin

Other lipid lowering medications	ezetimibe Omega 3 ethyl esters fenofibrate	
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Appendix 5: PHCC IRB



Department of Clinical Research
Primary Health Care Corporation
8th Floor, Tower 1
PO Box 26555
Al Meena Street
Doha, Qatar
Email: researchsection@phcc.gov.qa

Date: 22/04/2020

Dear Dr. Alaa Daban,

RE: Data Request Submission Decision Letter

Thank you for your recent submission titled 'Adherence to statin prescription guidelines for primary prevention of ASCVD among adult patients with Type 2 diabetes in PHCC; Audit based study' with reference number PHCC/DCR/2019/12/041.

This letter is to inform you that your submission was considered by PHCC Research Sub-Committee. The committee decided to approve the submission under the exempt category. The approval is valid for one year from date of this letter and is subject to the following conditions:

- You adhere to the principles of good research practice, prioritize patient's safety above all other concerns and ensure confidentiality and data protection throughout the study.
- You do not undertake other procedures and /or use participant materials or data outside of the scope of this present study, or future use beyond this study.
- You provide the Department of Clinical Research with a copy and the citation of your publication.
- In case of budget requests approval by PHCC; you adhere to acknowledging PHCC in your publication.

Please note:

- This approval is applicable only if you adhere to the above stated conditions and the committee reserves the right to revise its approval should this become necessary.
- This approval does not apply to any budget requests you may have made. If you have requested for a budget, it will be considered by Research Budget Working Group and a separate letter will be issued.

On behalf of the Research Sub-Committee, I wish you success in the conduct of this study and look forward to receiving your final report following its completion.

Yours Sincerely,

Dr Hamda Qotba
Chair, PHCC Research Sub-Committee



Appendix: 6 QU IRB



Qatar University Institutional Review Board QU-IRB

QU-IRB Registration: IRB-QU-2020-006, QU-IRB, Assurance: IRB-A-QU-2019-0009

DATE: April 14, 2021

TO: Alaa Daban, Mbbch, MRCP, MSc

FROM: Qatar University Institutional Review Board (QU-IRB)

PROJECT TITLE: 1726580-1Prevalence of statin prescription for primary prevention of arteriosclerotic cardiovascular disease among patients with type 2 diabetes in Qatar : A cross sectional study

QU-IRB REFERENCE #: QU-IRB 1524-E/21

SUBMISSION TYPE: New Project

ACTION: DETERMINATION OF EXEMPT STATUS

DECISION DATE: April 13, 2021

REVIEW CATEGORY: Exemption category # 3

Thank you for your submission of New Project materials for this project. The Qatar University Institutional Review Board (QU-IRB) has determined this project is EXEMPT FROM IRB REVIEW according to Qatar Ministry of Public Health regulations. Please note that exempted proposals do not require renewals however, any changes/modifications to the original submitted protocol should be reported to the committee to seek approval prior to continuation.

We will retain a copy of this correspondence within our records.

Documents Reviewed:

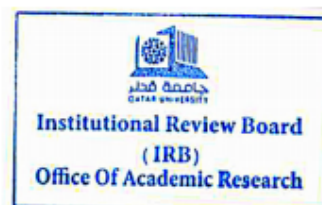
- Application Form - QU-IRB Brief Application Form_v3_01 Sept 2020_FINAL signed.pdf (UPLOADED: 03/4/2021)
- Letter - Approval letter_ Dr. Alaa - STAMPPED.pdf (UPLOADED: 02/25/2021)
- Proposal - Final PHCC Data Request Form11-10 feb 2020 adendum no scans.docx (UPLOADED: 02/25/2021)

If you have any questions, please contact QU-IRB at 4403 5307 or qu-irb@qu.edu.qa. Please include your project title and reference number in all correspondence with this committee.

Best wishes,

A handwritten signature in blue ink, appearing to read 'Ahmed Awaisu'.

Dr. Ahmed Awaisu
Chairperson, QU-IRB



This letter has been issued in accordance with all applicable regulations, and a copy is retained within Qatar University's records.