EVALUATION OF STATIN ASSOCIATION WITH HBA1C CONTROL, COGNITIVE FUNCTION AND HEALTHCARE PROFESSIONAL'S AWARENESS OF STATIN USAGE AMONG DIABETIC PATIENTS IN PENANG

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EVALUATION OF STATIN ASSOCIATION WITH HBA1C CONTROL, COGNITIVE FUNCTION AND HEALTHCARE PROFESSIONAL'S AWARENESS OF STATIN USAGE AMONG DIABETIC PATIENTS IN PENANG

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LIST OF ABBREVIATION

2-hr PPBS	2-hour Post Prandial Blood Sugar
3MS	Modified Mini-Mental State Examination
ACC	American College of Cardiology
ACE-III	Addenbrooke's Cognitive Examination-III
ACE-R	Addenbrooke's Cognitive Examination-Revised
ACEIs	Angiotensin-Converting Enzyme Inhibitors,
AD	Alzheimer's Disease
ADA	American Diabetes Association
ADRAC	The Adverse Drug Reactions Advisory Committee
AFORRD	Atorvastatin in Factorial with Omega-3 EE90 Risk Reduction in Diabetes
AHA	American Heart Association
AIDS	Acquired Immune Deficiency Syndrome
Akt or PKB	Protein Kinase B
ALT	Alanine Aminotransferase
ASHP	American Society of Health-System Pharmacists
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AR	Absolute Risk
ARBs	Angiotensin II Receptor Blockers
ARS	Adjusted R Squared
ASCOT-LLA	The Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm
ASCVD	Atherosclerotic Cardiovascular Disease

ASPEN	The Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus
AST	Aspartate Transaminase
BBB	Blood-Brain Barrier
BMI	Body Mass Index
BPH	Benign Prostatic Hyperplasia
CARDS	The Collaborative AtoRvastatin Diabetes Study
CCBs	Calcium Channel Blockers
CCDSS	The Canadian Chronic Disease Surveillance System
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CENTRAL	Cochrane Library Central Register of Controlled Trials
CG	Controlled Glycemia
CHD	Coronary Heart Disease
CI	Confidence Interval
CKD	Chronic Kidney Diseases
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CoQ10	Coenzyme Q10
CORALL	CholesteroL-Lowering effects of Rosuvastatin COmpared with Atorvastatin in patients with type 2 diabetes study
CPD	Continuing Professional Development
CPK	Creatine Phosphokinase
CrCl	Creatinine Clearance
CSIs	Cognitive Screening Instruments
CTT	Cholesterol Treatment Trialists

CV	Cardiovascular
CVA	Cerebrovascular Accident
CVD	Cardiovascular Disease
DALI	Diabetes Atorvastatin Lipid Intervention Study
DCM	Dilated Cardiomyopathy
DDM	Diabetic Dyslipidemia Management
DIT	Diabetes Intensification Therapy
DM	Diabetes Mellitus
DPN	Diabetic Peripheral Neuropathy
DR	Diabetic Retinopathy
DRPs	Drug-related problems
EAS	European Atherosclerosis Society
ED	Erectile Dysfunction
EPDET-HBCA	Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults.
ERR	Excess Relative Risk
ES-10Y	Estimated 10-Year Survival
FBG	Fasting Blood Glucose
FDA	The US Food and Drug Administration
FDS	Fremantle Diabetes Study
FH	Family History
FPG	Fasting Plasma Glucose
GC	Glycemic Control
GLUT4	Glucose Transporter Type 4
GPRD	General Practice Research Database.

GPs	General Practitioners
GTP	Guanosine Tri-Phosphate
HbA1c	Glycated Hemoglobin or Hemoglobin A_1c
HDI	High-Dose Intensity
HDL-C	High-Density Lipoprotein Cholesterol
HF	Heart Failure
HIV	Human Immunodeficiency Virus
HMG-CoA	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A
HMGCR	3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase
HOMA-IR	Homeostasis Model Assessment of Insulin Resistance
HPS	Heart Protection Study
hs-CRP	High-Sensitivity C-reactive Protein
HSD	Honestly Significant Difference
HTN	Hypertension
ICU	Intensive Care Unit
I-CVI	Item Content Validity Index
IDF	International Diabetes Federation,
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
IHD	Ischemic Heart Diseases
IIEF-5	International Index of Erectile Function Questionnaire-5
IL-6	Interleukin 6
IPSS	International Prostate Symptom Score
IQR	Interquartile Range
IR	Insulin Receptor

IRS	Insulin Receptor Substrate
J-CLAS	Japan Cholesterol Lowering Atorvastatin Study
JDS	Japan Diabetes Society
J-ECOH	The Japan Epidemiology Collaboration on Occupational Health
JPI-R	Jackson Personality Inventory–Revised
JUPITER	The Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin
KAP	Knowledge, Attitude, and Practice
LDI	Low-Dose Intensity
LDL-C	Low-Density Lipoprotein Cholesterol
LUTS	Lower Urinary Tract Symptoms
LV	Left Ventricular
M-ACE	Mini-Addenbrooke's Cognitive Examination
MCI	Mild Cognitive Impairment
MD	Mean Differences
MDI	Medium-Dose Intensity
MetS	Metabolic Syndrome
MHRA	The UK Medicines and Healthcare Products Regulatory Agency
MMSE	Mini-Mental State Examination
MMAS-8	8-Item Morisky Medication Adherence Scale
NADPH	Nicotinamide Adenine Dinucleotide Phosphate Hydrogen
NCEP	National Cholesterol Education Program
NG	Normoglycemic
NHANES	The National Health and Nutrition Examination Survey
NIDDM	Non-Insulin-Dependent Diabetes Mellitus

NIPH	Norwegian Institute of Public Health
NMUS	The National Medicines Use Survey
NNH	The Number Needed to Harm
NOD	New-Onset Diabetes
NOED	New Onset of Erectile Dysfunction
OR	Odds Ratio
OTC	Over-the-counter
PI3K	The phosphoinositide 3-kinase
PCP	Primary Care Physicians
PG	Postgraduate
PGQ	Postgraduate Qualification
PN	Peripheral Neuropathy
PROVE-IT TIMI 22	The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22 Trial
PV	Prostate Volume
Rac1	Ras-related C3 botulinum toxin substrate 1
RCANA	Research Committee of the American Neuropsychiatric Association
RCTs	Randomized Controlled Trials
RR	Relative Risk
SBG	Statin Benefit Group
SBP	Systolic Blood Pressure
SCC	Specialized Care Center
S-CVI	Scale-Content Validity Index
SD	Standard Deviation
SHF	Singapore Heart Foundation

SMD	Standardized Mean Difference
SNPs	Single Nucleotide Polymorphisms
TC	Total Cholesterol
THIN	The Health Improvement Network
TIA	Transient Ischemic Attack
UCG	Uncontrolled Glycemia
UDM	Uncontrolled Diabetes Mellitus
UK	United Kingdom
UKPDS	The United Kingdom Prospective Diabetes Study
USA	United States of America
USM	Universiti Sains Malaysia
VaD	Vascular Dementia
vs.	Versus
WHO	World Health Organization

PENILAIAN HUBUNGKAIT STATIN DENGAN KAWALAN HBA1C DAN FUNGSI KOGNITIF, KESEDARAN PROFESIONAL KESIHATAN TENTANG PENGGUNAAN STATIN DALAM KALANGAN PESAKIT DIABETES DI PULAU PINANG

ABSTRAK

Statin merupakan kelas ubat yang paling kerap dipreskripsi dan manfaatnya dalam terapi dislipidemia dan mengurangkan risiko penyakit jantung koronari telah dilaporkan dengan jelas. Namun begitu, kesan statin terhadap hasilan bukan kardiovaskular masih tidak jelas. Kajian ini bertujuan untuk menilai epidemiologi penggunaan statin dan kesannya terhadap kawalan hemoglobin glikasi (HbA1c) dan ketakmampuan kognitif dalam kalangan pesakit diabetes melitus jenis 2. Kajian ini juga bertujuan untuk mengukur kelaziman dan impak glisemia terkawal (CG) terhadap morbiditi dan anggaran kelangsungan hidup sepuluh tahun (ES-10Y). Sebagai tambahan, kajian ini juga bertujuan menilai pengetahuan, sikap dan amalan (KAP) ahli farmasi dan pakar perubatan tentang penggunaan statin dalam pesakit diabetik. Kira-kira 1400 orang pesakit dinilai dalam satu kajian keratan rentas di hospital Pulau Pinang, Malaysia, bagi menilai kelaziman preskripsi statin dan CG (HbA1c ≤7%) dinilai. Dalam kajian kohort prospektif, seramai 213 pengguna statin dan 187 bukan pengguna statin diikuti selama satu tahun untuk mengenal pasti kesan statin terhadap kawalan glisemik. Indeks Komorbiditi Charlson [Charson Comorbidity Index (CCI)] digunakan untuk mengira impak pembauran komorbiditi dan meramal ES-10Y dalam kalangan pesakit CG dan glisemia tidak terkawal (UCG). Ujian Kognitif Mini-Addenbrooke [Mini-Addenbrooke's Cognitive Examination

(M-ACE)] versi bahasa Melayu disesuai dan disahkan untuk menilai ketakmampuan kognitif dalam kalangan pesakit diabetes**.** Satu tinjauan KAP dibuat dan disahkan untuk meninjau kesedaran ahli penjagaan kesihatan tentang penggunaan statin dalam pengurusan dislipidemia diabetik (DDM). Daripada 757 orang pesakit, kira-kira 372 orang pesakit (49.1%) mempunyai UCG dan lebih daripada 102 daripada mereka (27.4%) mempunyai HbA1c melebihi 10%. Kira-kira 74.5% daripada pesakit diberikan terapi statin. Dalam analisis prospektif, seramai 400 pesakit diagihkan kepada kumpulan penerima rawatan, HbA1c 8.66 ± 1.77 dan kumpulan kawalan, HbA1c 7.89 ± 1.92 (*P* <0.001). Daripada 213 kumpulan yang menjalani terapi, kira-kira 145 orang pesakit (68.1%) mempunyai UCG. Daripada 187 pesakit dalam kumpulan kawalan, seramai 78 orang pesakit (41.7%) mempunyai UCG. Risiko relatif (RR) UCG bagi pesakit diabetes yang menggunakan statin adalah 1.63 [95% CI: 1.35-1.98]. Statin intensiti dos tinggi (HDI) mempunyai risiko UCG yang lebih tinggi, berbanding dengan intensiti dos sederhana (MDI) dan statin intensiti dos rendah (LDI) (RR: 1.26%, 95% CI: 1.04-1.54). Skor CCI untuk CG dan UCG masing-masing ialah 3.38 ± 2.38 dan 4.42 ± 2.70 (P: 0.001), ES-10Y adalah 62% dan 46.2% (P: 0.001). M-ACE menunjukkan bahawa RR ketakmampuan kognitif bersangkutan dengan penggunaan statin dalam pesakit diabetes adalah 1.72, (95% CI: 1.2 - 2.48). Dalam kajian KAP, doktor mewakili 78.5% dan ahli farmasi mewakili 21.5% responden. Hampir 21% daripada pasukan penjagaan kesihatan mempunyai kelayakan pascasiswazah (PGQ). Responden mempunyai pengalaman purata selama (5.3 ± 5.7) tahun. Pengetahuan responden mengenai statin adalah 75.2%. Skor amalan responden adalah 55.8%. Kira-kira 61% daripada mereka mempunyai sikap positif terhadap terapi statin dalam DDM manakala 19.5% daripada responden mempunyai sikap negatif dan 19.5% responden mempunyai sikap neutral. Skor purata

KAP bagi peserta yang memiliki PGQ jauh lebih tinggi daripada ahli penjagaan kesihatan tanpa PGQ; [(72.9 ± 18 berbanding 64.2 ± 15.6), (Z: -4.26, P: 0.001)]. Kepatuhan yang lebih terhadap panduan yang mencadangkan statin bagi pesakit diabetes jenis 2 sebagai kunci kepada terapi profilaksis adalah diperlukan. Kepatuhan ini memainkan peranan yang penting bagi memastikan kejayaan dalam memutuskan preskripsi dan penggunaan statin. Tambahan pula, usaha bagi memastikan pengoptimuman penggunaan dan preskripsi statin mampu membantu mencapai hasilan klinikal terapi statin yang lebih baik dalam DDM dan mengurangkan kesan sampingan berkaitan penggunaan statin. Walaubagaimanapun, masih terdapat keperluan untuk pembangunan professional berterusan (CPD) dan kelangsungan praktis lanjutan dalam pegoptimuman terapi statin.

EVALUATION OF STATIN ASSOCIATION WITH HBA1C CONTROL, COGNITIVE FUNCTION AND HEALTHCARE PROFESSIONAL'S AWARENESS OF STATIN USAGE AMONG DIABETIC PATIENTS IN PENANG

ABSTRACT

Statins are the most broadly prescribed class of medications, and their benefits in dyslipidemia therapy and diminishing the hazard for coronary heart disease (CHD) are well reported, but statins effects on non-cardiovascular outcomes are still unclear. This study aimed to assess the epidemiology of statins use and its effect on glycated hemoglobin (HbA1c) control and cognitive impairment among type 2 diabetic patients. Moreover, this study also aimed to measure the prevalence and impact of controlled glycemia (CG) on morbidity and estimated 10-year survival (ES-10Y). Furthermore, it meant to assess the knowledge, attitude, and practice (KAP) of pharmacists and physicians about statins use among the diabetic patients. About 1400 patients were scanned in a cross-sectional study at Hospital Pulau Pinang, Malaysia, the prevalence of statins prescription and CG (HbA1c $\leq$7%) was assessed. In a prospective cohort study, 213 statin users and 187 statin non-users were followed-up for one year to identify statin effect on glycemic control. Charlson Comorbidity Index (CCI) was used to calculate the confounding impact of comorbidities and to predict ES-10Y among CG and uncontrolled glycemia (UCG). Malay version of Mini-Addenbrooke's Cognitive Examination (M-ACE) was adapted and validated to assess the cognitive impairment among 280 diabetic patients. A KAP survey was constructed and validated to investigate the awareness of 200 healthcare providers about statins usage in diabetic dyslipidemia management (DDM). Of the 757 patients had an HbA1c test, about 372 (49.1%) cases had UCG, and more than 102 (27.4%)

of them had HbA1c >10%. About 74.5% of cases were prescribed with statin therapy. In the prospective analysis, 400 subjects, distributed among treatment cohort with HbA1c (8.66 ± 1.77), and control group with HbA1c (7.89 ± 1.92) (*P* <0.001). From 213 therapy group, about 145 (68.1%) patients had UCG. Of 187 patients in the control group, 78 (41.7%) patients had UCG. The relative risk (RR) of UCG in diabetic patients using statins was 1.63, (95% CI: 1.35–1.98). Statin treatment with high-dose intensity (HDI) had a higher risk of UCG, compared with medium-dose intensity (MDI) and low-dose intensity (LDI) statins (RR: 1.26, 95% CI: 1.04–1.54). CCI score was 3.38 ± 2.38 vs. 4.42 ± 2.70 (*P*-value: 0.001) and, ES-10Y was 62% vs 46.2% (*P*-value: 0.001) in CG vs. UCG respectively. M-ACE indicated that the RR of a cognitive impairment associated with statins utilization in diabetic patients is 1.72, (95% CI: 1.2 – 2.48). In the KAP study, the participants consist of 157 physicians and the 43 pharmacists. Nearly 21% of healthcare team had a postgraduate qualification (PGQ). The subjects had an average experience of (5.3 ± 5.7) years. Subjects' knowledge about statins was 75.2%. The score of respondents' practice was 55.8%. About 61% of them have a positive attitude about statins therapy in DDM. While only 19.5% of subjects have a negative attitude and same number of participants, have a neutral attitude. The KAP mean scores of participants with PGQ were significantly higher than healthcare without PGQ; [(72.9 ± 18 vs. 64.2 ± 15.6), *P*: 0.001]. The study determined that there was a dose-response association between statin therapy strength and glycemia control. The possibility of new-onset cognitive decline and the damage of existing cognitive deficits should be considered when prescribing a statin to patients. Statin therapy was associated with higher odds of adverse reactions compared with statins non-users but with substantial clinical benefit. However, patients with multiple medical co-morbidities and polypharmacy are at increased risk of adverse reactions from long-term statin utilization. More adherence to clinical recommendations that praise statin therapy for

diabetic patients as the key to CHD prevention therapy is required. This adherence may play a crucial role in ensuring success in the decision of statins prescribing and use. Moreover, exertions to guarantee optimization of the use and prescription of statin may help in accomplishing superior medical consequences of statin treatment in DDM and decrease side effects associated with statin usage. However, still, there is a necessity for more continuing professional development (CPD) and sustainable advanced practice in statin therapy optimization.

CHAPTER 1 : GENERAL INTRODUCTION

1.1 Statins

Statins (3-hydroxy-3-methyl-glutaryl-CoA reductase or HMG-CoA reductase inhibitors) are a class of medicines used to inhibit the enzyme HMG-CoA reductase and decrease cholesterol levels, which achieves an essential role in the synthesis of cholesterol in the liver, which creating about seventy percent of the total cholesterol (TC) in the body. Dyslipidemia is a well-reported risk factor for many cardiovascular diseases (Prospective Studies Collaboration et al., 2007, pp. 1829-39; Nelson, 2013, pp. 195-211).

Statins are the most widely provided category of drugs in the United States, and their benefits for reduction of low-density lipoprotein cholesterol (LDL-C) and reducing the risk for coronary heart disease (CHD) are well documented. Statins have been the backbone of pharmacotherapy for the treatment of dyslipidemia since their production (Cholesterol Treatment Trialists (CTT) Collaboration et al., 2010, pp. 1670-81). According to Taylor et al., (2013), statins therapy associated with a reduction of cardiovascular disease (CVD) and mortality rate in persons who are in elevated threat of CVD. The proof is substantial that statins are a useful therapy for CVD in the initial phases of illness (secondary prophylaxis) and persons at high hazard but lacking CVD (primary prophylaxis) (p. CD004816).

Dyslipidemia management no longer be modified to target specific LDL-C or non-high-density lipoprotein cholesterol (non–HDL-C) goals. Direct starting of statin treatment is not recommended for patients with class II-IV heart failure (HF) or those on maintenance hemodialysis as a routine (Stone et al., 2014, pp. S1-S45).

Starting statins therapy in secondary and primary protection at moderate- to high-intensity doses showed benefits in the individual with atherosclerotic cardiovascular disease (ASCVD), a person has an LDL-C of 4.9 mmol/L or higher. Moreover, statin has benefit in diabetic patients with age 40–75 years and an LDL-C of 1.8 – 4.9 mmol/L and without ASCVD. Furthermore statin has benefit in individuals with an LDL-C of 1.8 – 4.9 mmol/L and an evaluated 10-year ASCVD risk of 7.5% or more without diabetes or ASCVD (Cholesterol Treatment Trialists (CTT) Collaborators et al., 2010, pp. 1670-81; Taylor et al., 2013, p. CD004816).

1.1.1 Statins safety

The use of statins in cardiovascular events in patients with cardiovascular risks is efficient and safe (Cholesterol Treatment Trialists (CTT) Collaborators et al., 2008, pp. 117-25). In the United States (US), the labels of statin medicines, report information concerning glycemic effects, including diabetes mellitus and elevating in hemoglobin A1c or fasting blood sugar. These labeling changes had approved by the US Food and Drug Administration (FDA) in February 2012; depend mainly on evidence taken from two meta-analyses of randomized controlled clinical trials (Food and Drug Administration, 2012, para. 1). The earliest meta-analysis of statins matched with placebo, directed by Rajpathak et al., 2009, included patients from six trials and documented a little rise in risk (RR 1.13, 95% CI 1.03–1.23) for type 2 diabetes (pp. 1924-9). The second meta-analysis, showed the following year by Sattar and colleagues, investigated the consequence of statins usage on the risk of type 2 diabetes in 91 140 patients from thirteen trials (Sattar et al., 2010, pp. 735-42).

Sattar et al., (2010), showed that statins were accompanied with a nine percent increased risk of diabetes in participants receiving statins during an average follow-up period of approximately four years. The number required to treat over four years to result in one excess case of diabetes was 255. Moreover, in a meta-analysis of five trials, Preiss et al., (2011), also compared the risk of diabetes mellitus associated with higher potency and lower potency statins and reported that a twelve percent increased the risk of diabetes was related to higher potency statins higher than lower potency statins (pp. 2556-64).

Earlier 2015, the National Pharmaceutical Control Bureau issued a statement requesting all statin manufacturers in Malaysia to include the potential for increases in fasting blood glucose (FBG) and HbA1c with statins in the drug information leaflet in response to FDA report (p. 496). On the other hand, a limited study has been conducted in Malaysia regarding this warning label, but still there is some uncertainty whether such risk can also be detected in the Malaysian population or not (Atorvastatin Winthrop Tablet, 2015, para. 1).

Following a review of potential side effects, the UK Medicines and Healthcare Products Regulatory Agency (MHRA) (2009) decided that memory loss should be listed as a side effect in the product information for all statins (para. 1). Similarly, the US FDA (2012) required a declaration to be written in the drug label for all statins that there was a possible for cognitive side effects (para.1). This decision based on post-marketing event reports from persons of ill-defined memory loss or decline that appeared to be reversible after stopping statin therapy, and not because there was high-quality evidence for a causal link. Indeed, a later evaluation of FDA surveillance databases found the reporting degrees

of cognition-associated adverse events for statins to be similar to those of other drugs used in patients with atherosclerotic disease (as cited in Collins et al., 2016, pp. 2532-61).

1.1.2 Prevalence and burden cost of statins

Ministry of Health Malaysia, The National Medicines Use Survey (NMUS) states that: Lovastatin ranked 11th, simvastatin 18th and atorvastatin 20th in 2010, those have been steadily in the top forty drugs used (rank 15th, 20th, and 26th respectively in 2009) (Institute for Public Health, 2008, p. 783; Yusof et al., 2010a, pp. 21-28). While in Australia, atorvastatin ranked 1st and simvastatin 2nd in the medicine used, and in Norway, simvastatin ranked 1^{st,} and atorvastatin ranked 3rd (Australian Government Department of Health and Ageing, 2009, para. 1; NIPH, 2008, para. 1). The total expenses of lipid-modifying agents have increased from RM210.1 million in 2009 to RM328.9 million in 2010; an increase of more than 50% and it is 2nd ranked. Among the top 40 drugs, the highest spending was reported for amlodipine in 2009 (RM123.0 million) and simvastatin in 2010 (RM101.2 million). For these two drugs, more than 50% of the total spending was related to the private sector. The atorvastatin and simvastatin were for both years in the top 10 list of cost (Yusof et al., 2010b, pp. 29-35).

1.2 Diabetes Mellitus

Type 2 diabetes mellitus (Non-Insulin-dependent diabetes mellitus (NIDDM) or adult-onset diabetes) is a metabolic syndrome that is characterized by hyperglycemia in the context of insulin resistance and a relative shortage of insulin (Kumar, Fausto, Abbas, Cotran, & Robbins, 2005, pp. 1194-95). Type 2 diabetes is in contrast to diabetes type 1, in which there is a damage of islet cells in the pancreas leading to an absolute shortage of insulin (Masharani & German, 2011, para. 1). The classic symptoms are constant hunger excess urination and frequent thirst. About 90% of diabetic patients have type 2 diabetes. However, the other 10% represents type 1 diabetes and gestational diabetes.

1.2.1 Prevalence of Diabetes Mellitus

In 2015, around 415 million persons in the worldwide, or about nine percent of individuals in the age of work, are evaluated to have diabetes. Developing countries include 75% of diabetic patients. If these trends continue, by 2040 some 642 million people, or one adult in ten, will have diabetes mellitus. Approximately three new cases estimated to have diabetes every ten seconds or almost ten million per year (Kamenov, 2015, pp. 141-58; International Diabetes Federation, 2015, pp. 50-65).

In 2013, Malaysia was ranked between the top ten countries in the world with impaired glucose tolerance (IGT) prevalence (>15%) among the population aged 20 – 79 years as shown in Table 1.1. Impaired fasting glucose (IFG) along with, impaired glucose tolerance (IGT), is recognized as being a step former diabetes mellitus when blood glucose levels are higher than normal level. Thus, people with IGT are at elevated threat of getting type 2 diabetes. In more than one-third of individuals with IGT, blood glucose levels will

return to normal over a period of several years (International Diabetes Federation, 2013, p. 41; Shaw et al., 1999, pp. 399-402).

Table 1.1. Highest Ten Countries/Territories for Prevalence (%) of Impaired Glucose Tolerance (20-79 years), 2013 and 2035 (Guariguata, et al., 2014, pp. 137-49)

Country/ Territory	2013 (%)	Country/ Territory	2035 (%)
Kuwait	17.9	Poland	19.3
Qatar	17.1	Kuwait	18.1
United Arab Emirates	16.6	Qatar	17.4
Poland	16.5	United Arab Emirates	17.0
Bahrain	16.3	Bahrain	16.7
Malaysia	15.2	Malaysia	15.3
Hong Kong SAR	13.3	Hong Kong SAR	13.2
Nicaragua	12.9	Anguilla	13.0
Japan	12.6	Guadeloupe	13.0
Singapore	12.4	Macau SAR	12.9

While the burden of diabetes continues to increase in Malaysia, the overall prevalence of diabetes in Malaysia was around twenty-three percent, where eleven percent was known diabetes, and twelve percent was new diabetes. Diabetes mellitus (DM) is a central public health issue in Malaysia and has been shown to be closely related to enhanced premature and preventable mortality, as well as macro and microvascular complications such as amputation heart disease, blindness, end-stage renal failure, and stroke (National Diabetes Registry Report, 2013, para. 1).

1.2.2 HbA1c

HbA_1c: A blood examination can quantify the amount of glycosylated hemoglobin in the blood. The assessment of HbA1c gives an indication about the mean of the level of an individual's glycemia for the last three months before the investigation. HbA1c can benefit in the evaluation to what extent an individual's glycemia is being within the target over time or not. Glucose molecules in the blood typically become cemented to hemoglobin molecules - this means the hemoglobin has developed into glycosylated (also reported as hemoglobin A_1c or HbA1c). As an individual's blood sugar becomes higher than optimal blood glucose, more of the person's hemoglobin will become glycosylated. The glucose rests fixed to the hemoglobin for the lifecycle of the red blood corpuscles, or around sixty to ninety days (Guide to HbA1c, 2015, para. 1).

Monitoring of glycosylated hemoglobin levels depends on the clinical needs of diabetic patient and his history of HbA1c control. The best practice in hemoglobin A1c monitoring is once per three months if trying to get better management or once per six to nine months if good control achieved and maintained (Guide to HbA1c, 2015, para. 1).

1.2.3 Uncontrolled hyperglycemia

Hyperglycemia is the circulation of an increased quantity of glucose higher than 11.1 mmol/l (200 mg/dl) in the plasma of blood. The symptoms of diabetes may not start to become observable until even higher values such as 15-20 mmol/l (270-360 mg/dl). However, chronic levels exceeding 7mmol/L (125 mg/dl) can produce organ damage (American Diabetes Association, 2014, pp. S81-S90).

Uncontrolled diabetes mellitus or uncontrolled glycemia (UCG) is a diagnosis, which indicates that the person's blood glucose level is not kept within normal levels by his or her current therapy regimen; it will be determined by measuring HbA_1c. For non-diabetics, the regular reading is (3.5 – 5.5%). For diabetic people, an HbA_1c level of 6.5% is considered a good control, although some individuals may desire their numbers to be nearer to that of non-diabetics. American Diabetes Association (ADA) suggested that HbA_1c more than seven percent is seen as UCG. The target of HbA1c, in general, is less than seven percent, designated according to the clinical practice and the predictable decrease in the diabetic complications through the treatment (American Diabetes Association, 2018, pp. S55-S64).

1.3 Cognition impairment

Cognition is the conceptual achievement or procedure of receiving information and thoughtful to take action, throughout, understanding, feeling, and believed. It encompasses processes such as attention, learning, memory, and working memory, problem-solving and decision-making, computation, comprehension, evaluation, judgment, reasoning, and production of language (Oxford Dictionary, 2016, para. 1). Cognitive impairment is when a person has a problem with focusing, education new things, memorizing, building judgments or taking a decision that may affect their daily life. Cognitive deficit arrays from minor to severe. With mild cognitive impairment (MCI), persons may start to detect alterations in cognition functions, without disturbing their daily doings. Critical levels of cognitive decline can result in down the capability to comprehend the sense or meaning of something and capacity to dialog or using a pen, leading to the incapacity to depend on himself (Centers for Disease Control and Prevention, 2011, para. 1).

Cognitive impairment is well-defined as a comprehensive term to interpret any characteristic that operates as an obstacle to the cognition procedure (Stanley, Ward & Enns, 1999, p. 9). The term may refer to deficits in learning disorders, or it may illustrate drug-induced cognitive/memory disability, such as that seen with benzodiazepines and alcohol (Kalachnik, Hanzel, Sevenich & Harder, 2002, pp. 376-410). It typically mentions as conflicting to the changed level of awareness, which may be severe and recoverable. Brain wounds may cause cognitive impairment, mental diseases or neurological conditions (Hockenbury & Sandy, 2004, para. 1). MCI has been proposed as a term for a

confined area among healthy aging and dementia, especially Alzheimer's disease (AD) (Hänninen, Hallikainen, Tuomainen, Vanhanen, & Soininen, 2002, pp. 148-54).

1.3.1 Epidemiology of mild cognitive impairment (MCI)

Prevalence evaluates of mild assorted from sixteen percent to twenty percent for the most of the analyzed research. A few studies had a very high estimation that could be due to issues with non-participation or elements particular to the survey method (Sachdev et al., 2012, pp. 854-65). Estimates from studies conducted in urban sites, multiethnic cohorts, and in clinic-based studies were also at the higher end of the spectrum (Roberts & Knopman, 2013, para. 1).

1.4 Complications of Diabetes

Diabetes mellitus is a category of chronic disorders characterized by high blood glucose (hyperglycemia). The advanced medical therapy uses different ways of lifestyle modification and pharmaceutical interventions aimed at controlling and preventing hyperglycemia. In addition to confirming enough delivery of sugar to the body tissues, treatment of diabetes attempts to decrease the likelihood that hyperglycemia harms the tissues of the body. The significance of body protection from uncontrolled glycemia cannot be inflated; al the consequences of hyperglycemia on the vascular-tree of the body are the main basis of illness and death equally in all type of diabetes. The harmful effects of hyperglycemia are classified into microvascular complications (diabetic nephropathy, neuropathy, and retinopathy) and macrovascular disorders (coronary artery disease, peripheral arterial disease, and stroke). It is crucial for clinicians to comprehend the relationship between diabetes and vascular disease because the diabetes prevalence continues to increase in the world, and the clinical equipment for primary and secondary prevention of these complications are also expanding (Fowler, 2008, pp. 77-82).

Benign prostatic hyperplasia (BPH) is a non-cancerous increase in the prostate size. Symptoms may involve frequent urination, trouble starting to urinate, weak stream, inability to urinate, or loss of bladder control. Complications can comprise bladder stones, urinary tract infections, and chronic renal problems (Kim, Larson & Andriole, 2016, pp. 137-51). Using a histologic definition, the prevalence of BPH is higher than fifty percent by age sixty and almost ninety percent by age eighty-five (McConnell, Barry, & Bruskewitz, 1994, para. 1). A total of thirty-one prevalence rate estimations from twenty-five countries were identified. The combined prevalence estimates showed that the

lifetime prevalence of BPH was about twenty-six percent (95% CI: 22.8–29.6%) (Lee, Chan, & Lai, 2017, pp. 1-10).

Cataract is well defined as opaqueness of the lens clarity in the eye that decreases the extent of received lightness and leads to worsening of eyesight (Gupta, Rajagopala, & Ravishankar, 2014, pp. 103-10). The predominance of cataract without operation in persons with age of sixty or older was fifty-three percent in south India and fifty-eight percent in north India.

The predominance of cataract in Koreans more than forty years of age was forty percent (Yoon, Mun, Kim, & Kim, 2011, pp. 421-33). In a National Eye Investigation, cataract was the main reason for thirty-nine percent of the two-sided loss of vision in Malaysia, whereas cataract responsible for sixty percent of the loss of sight and severe optical deficiency in Hanian region, China (Zainal, Ismail, Ropilah, & Elias, 2002, pp. 951-56; Li, Liu, Liang, & Zhang, 2013, pp. 2176-83). In Indonesia, the predominance degree of any cataract for persons with age from twenty-one until twenty-nine was about one percent, snowballing to eighty-eight percent for persons with age more than sixty years old (Husain, Tong, Fong, Cheng, & How, 2005, pp. 1255-62; Thevi & Reddy, 2016, pp. 1-13).

Chronic Obstructive Pulmonary Disease (COPD) is a progressive lung disease that makes a person feels increasingly difficult to breathe, breathlessness, excessive phlegm production, as well as a chronic cough. The condition mostly occurs in persons aged more than forty years and is mainly caused by smoking and smog in the atmosphere. (World Health Organization, 2015, para. 1). The prevalence of moderate to severe COPD in

Malaysia is nearly five percent which interprets to more than four-hundred and forty thousand patients (Ismail, 2009, pp. 250-56).

Diabetic retinopathy (DR) is a microvascular complication that results from prolonged UCG (Ramachandran, Snehalatha, & Viswanathan, 2002, pp. 1471-76). DR is characterized by varying degrees of microaneurysms, hemorrhages, hard exudates, cotton wool spots, venous changes, new vessel formation, and macular thickening. It can involve the peripheral retina, the macula, or both. Diabetic eye illness is the main reason for blindness in the Malaysian persons at the age of work. The prevalence of DR in Malaysia has been reported to range from forty-four to forty-nine percent (Tajunisah, Nabilah & Reddy, 2006, pp. 451-56). The United Kingdom Prospective Diabetes Study (UKPDS), in which thirty-nine percent of men and thirty-five percent of women had DR at the time of diagnosis (Mohd Ali, Draman, Mohamed, Yaakub & Embong, 2016, pp. 353-58).

Erectile dysfunction (ED) is a situation in which a male is unable to achieve or maintain a penile erection firm enough for satisfactory sexual intercourse (Nunes, Labazi & Webb, 2012, pp. 163-70). ED occurs in about 12% of men younger than 60, about 22% of men age 60 to 69 and 30% of men age 70 or older (Heidelbaugh, 2010, pp. 305-12). Data from the Massachusetts Male Aging Study (MMAS) stated that 52% of men aged 40-70 years, reported erectile dysfunction in Massachusetts, United States (Muneer, Kalsi, Nazareth, & Arya, 2014, pp. 1-9).

Peripheral neuropathy (PN) is a neuron illness. It can result in discomfort, faintness, numbness, sting, and tingling. The signs typically start in the lengthiest body nerves and so primary distress the legs and fingers. PN is sometimes called the “stocking-

glove" pattern. The symptoms usually extend slowly and evenly up the arms and legs. Other body parts might also be influenced. Most individuals who develop PN are over the age of fifty-five years. But persons can be affected at any age (American Academy of Neurology, 2012, para 1). Peripheral neuropathy is a significant cause of disability worldwide. Diabetes is the primary common cause of neuropathy, accounting for fifty percent of cases (International Diabetes federation, 2011, para. 1). Over half of diabetic people develop neuropathy, and twenty percent of type 2 diabetic patients have diabetic peripheral neuropathy (DPN) at diabetes presentation. DPN is a significant cause of reduced quality of life due to pain, sensory loss, gait instability, fall-related injury, and foot ulceration and amputation (Stino & Smith, 2017, pp. 646-55).

1.5 Statement of the problem

Current evidence indicates that statins enhance the incidence of diabetes; however, the relationship between glycemic control in patients with established diabetes and statins has not been well-characterized (Erqou, Lee, & Adler, 2014, pp. 2444-52). There are drawbacks in the prior research that have investigated the diabetogenic effect of statins therapy and its impact on HbA_1c control in Malaysia. Investigating the impacts of statin therapy on glycemia controlling in diabetic persons is worthy since statins are consequently prescribed to most of the diabetic patients.

Moreover, the Mini-Addenbrooke's Cognitive Examination (M-ACE) is a novel assessment tool for cognition deficit developed in 2015 (Hsieh et al., 2015, pp. 1-11). Until the date of starting the present study, M-ACE was not translated or adapted to Malay. Further, M-ACE was not applied among the Malaysian population to detect cognitive decline in diabetic patients under statin therapy.

The association between diabetic complications and statins therapy has not been reported in Malaysia, thus deserves further study. Moreover, the need for evaluation of healthcare awareness about statins use and its adverse effects. There is a requirement of investigation the impact of postgraduate qualification on the healthcare awareness of statins usage in the management of diabetic dyslipidemia.

Medication safety is always very important issue especially with the statins, for many reasons. First, and perhaps the most important factor, statins are frequently prescribed. Statins are the single major prescribed category of drugs, in dollar value, in the United States today. Second, they are prescribed for a prolonged duration of patient'

life. Over the many years that a typical patient takes a statin, there are many chances for adverse events, including unexpected changes in the patient's health status. A third and critical factor is that statins are most commonly used in middle-aged or elderly patients, who tend to be prescribed many other medicines for other diseases. The advanced age heightens safety concerns, both because the polypharmacy typical of these age groups significantly increases the overall risk of drug-drug interactions. Also because many of the diseases prevalent in older patients contribute to drug safety concerns, and finally, because of advanced age itself, probably increases the risk of drug side effects and toxicity (Brinton, 2004, para. 1).

1.6 The significance of the study

The majority of studies about the effect of statin on HbA1c control and diabetes complications were conducted in developed countries, but the studies of diabetogenic impacts of statin in Malaysia are still limited. Research results on the epidemiology and clinical characteristics of diabetogenic effects of statins in Malaysia can be used for better control of HbA1c, FBG, and avoidance the complications of diabetes. A unique feature of this study population can also be used for participation in global trails and a better understanding of the diabetogenic effect of statins.

Limited data are available about the effect of statins on HbA1c control in Malaysia, and there is probably no information on the baseline characteristics, the comparison between different doses, various members of statins, cognition impairment and diabetic complication among statins users. This information can assist in distinguishing between the overall effects of different statins members.

Also, there are no updated data on the prevalence of statins utilization in Malaysia. These results can help to improve evidence-based treatment by achieving the optimal benefit from statins while minimizing their side effects and diabetes complications. Moreover, controversial data are available on the consequences of statins utilization on the diabetic complications; information from the study can assist in clearing the situation and improve the quality of life for the patients. Obtaining these data can increase the awareness about statins effects on HbA1c and diabetic complications, and help in the quick detection and prevention of this problem.

If diabetic patients decrease their HbA_1c level by one percent, there is about nineteen percent reduction in cataract extractions, sixteen percent decrease in heart failure and forty-three percent reduction in amputation or death due to peripheral vascular disease (Guide to HbA1c, 2015, para. 1). Therefore, the optimization of statins therapy will reflect on more achievement of HbA1c control that result in the reduction of diabetic complication and increase the survival rate among the diabetic patients.

Identifying the effect of statins use on the HbA1c controlling in Malaysian, Chinese and Indian ethnicity. The outcomes of the study may play as a base for thinking about the pharmacogenetic effect of statins among various ethnicity of diabetic patients.

The findings may be a key for thinking about the alternative of statins drugs to decrease the incidence rate of new onset diabetes mellitus and optimize the glycemic control, which reduces the suffering of patients from the complications of diabetes mellitus. The decline of statins using, the reduction of diabetes incidence and achieving blood glucose target will result in a decrease of the direct and indirect cost of diabetes illness. Results will help in patient care improvement, increasing patient quality of life and survival rate.

Mild cognitive impairment (MCI) is a stage that is potentially amenable to interferences that may avoid more deterioration toward dementia; the stage of cognitive dysfunction that has a more massive effect on the everyday behavior. The study may afford a more understanding of MCI and share to early detection of subjects with MCI. Patients with MCI may benefit from interventions that will decrease their risk of progression to dementia and may be eligible for treatment with disease-modifying drugs

that reverse previous damage or prevent further decline when such therapy become available (Roberts & Knopman, 2013, pp. 753-72).

The Malay version of the M-ACE is a brief, reliable, and very useful screening tool for the assessment of cognitive deficiency and has shown to discriminate between MCI and dementia. This study is among the earliest to apply the M-ACE to a Malay-speaking population. The Malay version of the M-ACE can use as a tool for cognitive examination in the outpatients setting, highly crowded clinics and research.

The study explored the prevalence of cognition impairment, benign prostatic hyperplasia (BPH), cataract, COPD, diabetic retinopathy, erectile dysfunction (ED) and peripheral neuropathy incidence among type 2 diabetic outpatients in the Malaysian population. Moreover, the study revealed the effect of statins on cognitive impairment, BPH, cataract, COPD, DR, ED, and PN which help in the optimization of statins therapy in diabetic dyslipidemia management (DDM).

The evaluation of awareness and knowledge of the healthcare team about statins use and its adverse effects, which can be a base for future training and continuous professional development.

1.7 Research questions

- What is the prevalence of uncontrolled glycemia and statins prescribing amongst type 2 diabetic persons?
- Does statin utilization increase or decrease HbA1c and fasting blood glucose among diabetic people?
- Do the various doses of statins have the same effect on HbA1c?
- Do the various members of statins have the same impact on HbA1c?
- Does the HbA1c control have an impact on morbidity and estimated 10-year survival (ES-10Y)?
- What is the effect of statins on cognition among diabetic individuals?
- What is the prevalence of non-cardiovascular clinical outcomes and the influence of statins on non-cardiovascular clinical outcomes among diabetic patients?
- What is the level of healthcare professionals' awareness toward the use of statins in the management of diabetic dyslipidemia?
- What is the effect of postgraduate qualification, gender and the type of job (pharmacist vs. physician) on the awareness of statin use in the management of diabetic dyslipidemia?

1.8 Objectives

1.8.1 Primary objectives

1.8.1.1 To assess the effect of statins usage on HbA_1c control and fasting blood glucose.

1.8.1.2 To evaluate the healthcare providers' awareness and attitude about statins use.

1.8.2 Secondary objectives

1.8.2.1 To match the influences of different dosages of statins (High, moderate and low intensity) on HbA1c control.

1.8.2.2 To explore the effect of the various members of statins (for equivalent doses) on HbA1c control.

1.8.2.3 To evaluate the impact of glycated hemoglobin control on morbidity and estimated 10-year survival (ES-10Y).

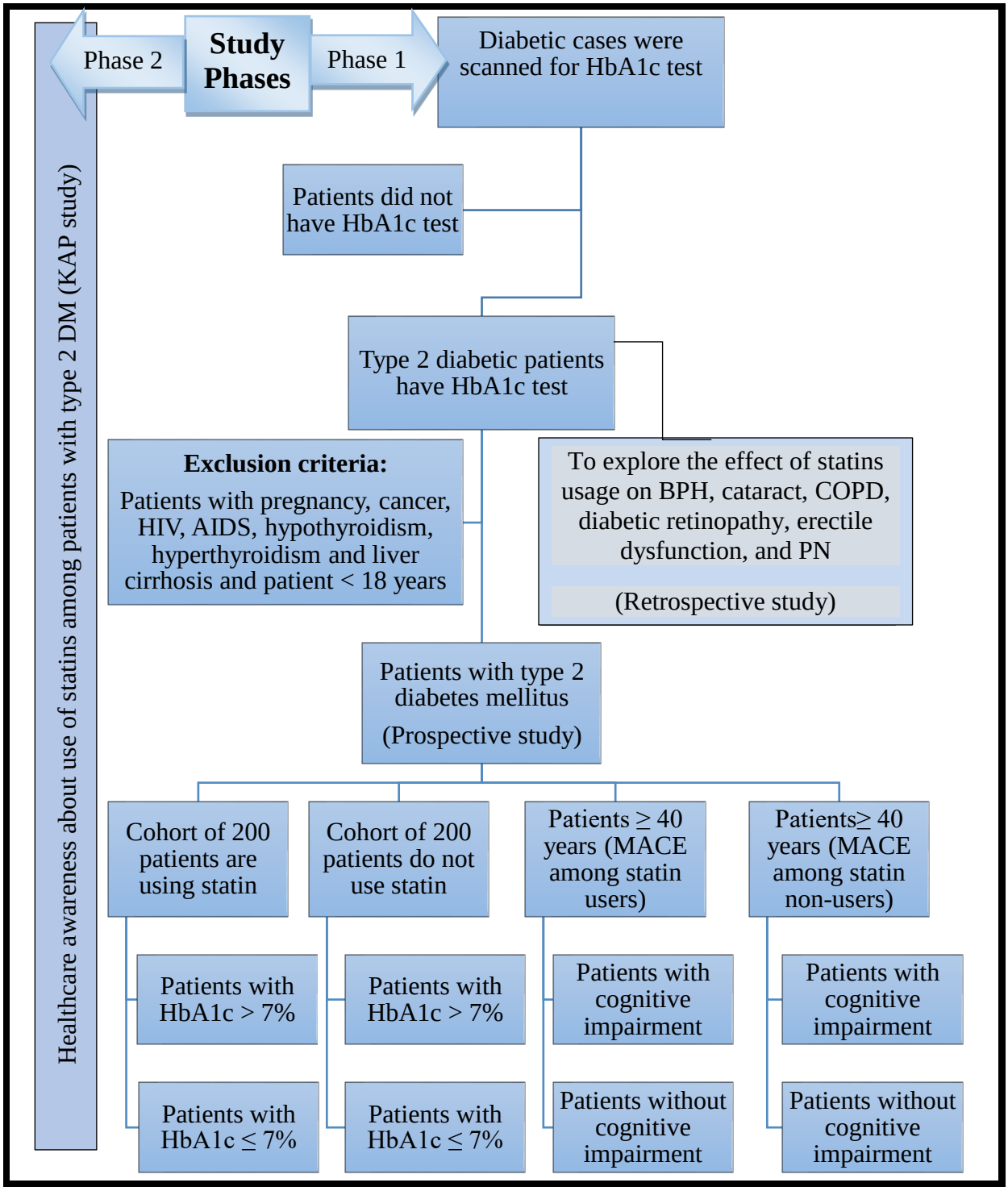
1.8.2.4 To assess the effect of statin use on cognitive function.

1.8.2.5 To determine the effect of statins on diabetic complications incidence among type 2 diabetic outpatients.

1.9 Justification of the study

The present study was conducted to detect the gap in the adherence of healthcare providers by clinical treatment guidelines in the management of diabetic dyslipidemia. The findings from the survey will enable the policy makers to identify the zones where improvement should be highlighted regarding the application of treatment guidelines, recommendations, and statins therapy optimization. If these gaps are addressed, hopefully, this would lead to reduced incidence of diabetic related complications and decrease the cost of illness. The study also sought to afford baseline data on the prevalence of diabetic complications associated with statins therapy in an understudied area.

These data can be considered as a reference point against which the effectiveness of any future intervention to improve diabetic and cognitive impairment management can be measured. Lastly, gaps in healthcare awareness, attitude and practice were identified, and these will form the basis of continuing professional education and training to improve the pharmacological interventions and practice of the healthcare providers. The net result of the findings will reflect on improving the rational use of medications, advancing patient care, advanced practice, and sustainable improvement of patients' quality of life.



AIDS: Acquired immune deficiency syndrome, BPH: Benign prostatic hyperplasia, COPD: Chronic obstructive pulmonary disease, DM: Diabetes mellitus, HbA1c: Glycated hemoglobin, HIV: Human immunodeficiency virus, PN: peripheral neuropathy.

Figure 1.1. The framework of the thesis

CHAPTER 2 : LITERATURE REVIEW

Statin treatment is the keystone of primary and secondary prevention of cardiovascular disease (The Emerging Risk Factors Collaboration, 2010, pp. 2215-22). Diabetes is a significant hazard factor for cardiovascular diseases (CVD) and is recognized as a cardiovascular (CV) risk equivalent. Therapy guidelines indicate that most of the diabetic patients would benefit from statin therapy (Cholesterol Treatment Trialists' (CTT) Collaborators et al., 2008, pp. 117-25; National Cholesterol Education Program, 2002, pp. 3143-421; Rocco, 2012, pp. 883-93). Recent clinical recommendations from the American College of Cardiology and the American Heart Association stated that all diabetic patients who are forty to seventy-five years of age should be placed on moderate or high-intensity statin treatment to avoid or delay CVD (Stone et al., 2014, pp. S1-45).

Although their crucial role in the avoidance and postponement of CVD, there is proof proposing that statins deteriorate blood glucose level and raise the hazard of emerging type 2 diabetes by around ten to twelve percent (Sattar et al., 2010, pp. 735-42; Maki et al., 2014, pp. S17-29). The consequence of statins therapy on the occurrence of diabetes seems to vary by dosage and kind; high dosages result in a higher threat than lesser dosages (Preiss et al., 2011, pp. 2556-64). Moreover, rosuvastatin and atorvastatin are concomitant with a higher hazard than pravastatin (Carter et al., 2013, para. 1). On the other hand, the consequence of statins on HbA1c and blood glucose in persons with pre-existing diabetes is indistinct.