PROSPECTIVE STUDY ON STATINS EFFECT ON CLINICAL OUTCOMES AMONG NON-DIALYSIS CKD PATIENTS: A COMPARISON BETWEEN A HOSPITAL IN MALAYSIA AND SAUDI ARABIA

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by

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DEDICATION

To my appreciated father "Mohammad Nimer Kharshid"

To my dearest mother

To my lovely kids "Retal and Rayyan"

To my dearest Family "Khetam, Saed, Samer, Maryam, Khadeeja, Areej"

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LIST OF ABBREVIATIONS

4D	Die Deutsche Diabetes Dialyze
α	Cronbach's alpha
ηp2	Partial Eta-Squared
A10	Atorvastatin 10
A20	Atorvastatin 20
A40	Atorvastatin 40
AEs	Adverse Effects
AGREE	Appraisal of Guidelines for Research and Evaluation (AGREE)
AKI	Acute Kidney Injury
ALB	Albumin
ALT	Alanine transferase
ALP	Alkaline Phosphatase
ANOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATPIII	Adult Treatment Panel III
AURORA	A study to Evaluate the Use of Rosuvastatin in subjects On Regular Haemodialysis: An Assessment of survival and Cardiovascular Events
BILI	Bilirubin
BMI	Body Mass Index
BP	Blood Pressure
CABG	Coronary Artery Bypass Grafting
CARE	Cholesterol and Recurrent Events
CBAHI	The Central Board for Accreditation of Healthcare Institutions

CHD	Coronary Heart Disease
CI	Confidence Interval
CK	Creatinine Kinase
CKD	Chronic Kidney Disease
CL	Chloride
ClinROs	Clinician-Reported Outcomes
CME	Continuous Medical Education
CNS	Central Nervous System
COPD	Chronic Obstructive Pulmonary Disease
CPG	Clinical Practice Guidelines (CPG)
CRC	Clinical Research Centre
CVD	Cardiovascular Disease
DG	Development Group
DKD	Diabetic Kidney Disease
EBM	Evidence Based Medicine
EF	Energy/fatigue
Egfr	Estimated Glomerular Filtration Rate
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESRD	End-Stage Renal Disease
ESRF	End Stage Renal Failure
FACT-G	Functional Assessment of Cancer Therapy-Generic
FBS	Fasting Blood Sugar
GFR	Glomular Filtration Rate
GGT	Gamma-Glutamyl Transpeptidase

GH	General Health
GLOB	Globulin
GPs	General Practitioners
HbA1C	Glycated Haemoglobin
HCP	Health Care Professional
HD	Hemodialysis
HDL-C	High-Density Lipoprotein Cholesterol
Hgb	Hemoglobin
HIV	Human Immunodeficiency Virus
HMG CoA	3-hydroxy-3-methylglutaryl preventing coenzyme A
HPP	Hospital Pulau Pinang
HRQoL	Health Related Quality of Life
HTA	Health Technology Assessment
I	Immediately
ICC	Intraclass Correlation Coefficient
IRB	Institutional Review Board
IQR	Inter Quartile Range
K	Potassium
KAP	Knowledge, Attitude and Practice/Perception
KAP-O	Knowledge, Attitude, Practice/Perception and Outcomes
KDIGO	The Kidney Disease: Improving Global Outcomes
KDQOL	Kidney Disease Quality of Life
KEEP	Kidney Early Evaluation Program
KSA	The Kingdome of Saudi Arabia
KT	Kidney Transplant

LDL-C	Low-Density Lipoprotein Cholesterol
LIPID	Long-Term Intervention with Pravastatin in Ischemic Disease
LVAD	Left Ventricular Assist Device
M	Month
M	Malay
MAP	Mean Arterial Pressure
MCS	Mental Composite Summary
MDRD	Modification of Diet in Renal Disease
MH	Mental Health
MoH	Ministry of Health
MOS	Medical Outcomes Study
Na	Sodium
NASH	Nonalcoholic Steatohepatitis
NKDEP	National Kidney Disease Education Program
NKF KDOQI	National Kidney Foundation Kidney Disease Outcomes Quality Initiative
NMRR	National Medical Research Register
NS	Non-Statins
ObservROs	Observer-Reported Outcomes
OR	Odds Ratio
oxLDL	Oxidised Low-Density Lipoprotein
P	Pain
PCS	Physical Composite Summary
PF	Physical Functioning
PLANET	The Prospective Evaluation of Proteinuria and Renal Function in Diabetic Patients with Progressive Renal Disease

PLT	Platelets
PROMIS	Patient-Reported Outcomes Measurement Information System
Qol	Quality of Life
RBCs	Red Blood Cells
RC	Review Committee
RCTs	Randomized Controlled Trials
RE	Role functioning/emotional
RM	Malaysian Ringgit
Rm-ANOVA	Repeated Measures Analysis of Variance
RP	Role functioning/physical
RR	Relative Risk
RRT	Renal Replacement Therapy
S10	Simvastatin 10
S20	Simvastatin 20
S40	Simvastatin 40.
SD	Slandered Deviation
SF	Social Functioning
SF-36	Short Form-36
SFHP	Security Force Hospital Program
SHARP	Study of Heart and Renal Protection
SPSS	Statistical Package for The Social Sciences
STD	Sexually Transmitted Disease
SWB	Subjective Well-Being
TB	Tuberculosis
TC	Total Cholesterol

TG	Triglycerides
TP	Total Protein
TV	Television
U.K.	United Kingdome
UB	Blood in Urine
UP	Protein in Urine
UpH	Urine Ph
US	United States
WBCs	White Blood Cells
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life Assessment

KAJIAN PERSPEKTIF KEATAS KESAN STATIN TERHADAP DAPATAN KLINIKAL DALAM KALANGAN PESAKIT GINJAL KRONIK – TANPA DIALISIS: PERBANDINGAN DIANTARA SEBUAH HOSPITAL DI MALAYSIA DAN ARAB SAUDI

ABSTRAK

Penyakit Ginjal Kronik (CKD) adalah kebimbangan kesihatan global yang merupakan sebahagian besar daripada beban penyakit di seluruh dunia. Untuk mengawal kemajuan CKD, banyak strategi telah dicadangkan. Walau bagaimanapun, masih banyak soalan yang perlu dijawab dalam segmen amalan klinikal ini terutamanya di negara-negara seperti Kerajaan Arab Saudi (KSA) dan Malaysia. Sebagai contoh, penggunaan statin untuk pesakit CKD masih kontroversi kerana bukti yang bercanggah. Juga, Kualiti Hidup Kehidupan (HRQOL) pesakit CKD bukan dialisis tidak dinilai di negara yang disebut dahulu. Tambahan pula, Sikap dan Persepsi Pengetahuan (KAPs) Profesional Penjagaan Kesihatan (HCP) di Malaysia dan KSA belum dinilai walaupun HCP terutamanya ahli nefrologi merupakan teras utama pelaksanaan garis panduan CKD yang sesuai. Oleh itu, matlamat kajian ini adalah untuk mengkaji kesan renoprotektif dan komplikasi pelbagai dos / jenis statin (lengan A kajian), untuk menilai kualiti hidup yang berkaitan dengan kesihatan pesakit ND-CKD Malaysia dan Saudi (lengan B), dan menilai ahli farmasi dan pakar perubatan dan kesedaran mengenai penggunaan statin dalam pesakit CKD di hospital dan penjagaan kesihatan Malaysia dan hospital Saudi (arm C). Bagi lengan A (penggunaan statin), 455 pesakit dari Hospital Pulau Pinang (HPP), Pulau Pinang, Malaysia, dan 431 pesakit dari Program Keselamatan Angkatan Keselamatan (SFHP) di Riyadh, KSA yang mengambil statin (jenis dan dos yang berlainan) dimasukkan dan kriteria

pengecualian kajian dimasukkan. Reka bentuk prospektif kajian yang diamati telah diterima pakai di mana peserta kajian diikuti pada garis dasar, selang tiga, enam, dan sembilan bulan. Hanya atorvastatin 40 mg menunjukkan kalium yang lebih tinggi dan tahap urea yang jauh lebih rendah daripada plasebo. Selain itu, tidak terdapat perbezaan yang signifikan dalam kesan Simvastatin 20mg apabila digunakan dalam populasi Malaysia dan Saudi. Bagi lengan B (HRQOL), seramai 526 orang pesakit tidak dialisis di kalangan pesakit CKD di Malaysia dan 301 pesakit Saudi dimasukkan untuk mengisi borang soal selidik yang disahkan SF-36. Reka bentuk penyelidikan rentas keratan telah digunakan untuk menilai kesan CKD pada skor HRQOL di kalangan pesakit CKD dialisis di HPP di Pulau Pinang, Malaysia, dan SFHP di Riyadh, KSA. Umur muda, tempoh dan peringkat CKD yang lebih rendah, pendapatan lebih tinggi, dan tahap pendidikan yang lebih tinggi semuanya dikaitkan dengan skor HRQOL yang lebih tinggi. Kesimpulannya, pemerhatian ini menunjukkan kesan kuat ND-CKD pada HRQOL. Kajian lanjut untuk merancang dan menilai campur tangan yang berpotensi bagi peningkatan HRQOL dalam pesakit ND-CKD adalah wajar. Untuk lengan C (KAPs), Reka bentuk rentas keratan dipakai menggunakan soal selidik sendiri yang dibina dan disahkan sebelum kajian dijalankan. Soal selidik diedarkan kepada 187 HCP di SFHP di Riyadh, Arab Saudi, dan 122 HCP di HPP di Pulau Pinang, Malaysia. Jurnal perubatan telah dipilih sebagai sumber asas untuk maklumat CKD yang dikemas kini di Malaysia dan KSA (masing-masing 30% dan 39%). Lebih daripada 90% daripada mereka bersetuju dengan keperluan rujukan awal pesakit CKD kepada seorang ahli nefrologi. Umur yang lebih tua, doktor pakar, pengalaman lebih lama, gaji tertinggi secara konsisten berkaitan dengan skor yang lebih tinggi. Akhir sekali, ada ruang untuk penambahbaikan program CME, dan pengetahuan HCP

mengenai CKD dan penggunaan statin. HCP dari kedua-dua negara mempunyai sikap / persepsi positif terhadap penggunaan statin dalam meningkatkan hasil pesakit CKD.

PROSPECTIVE STUDY ON STATINS EFFECT ON CLINICAL OUTCOMES AMONG NON-DIALYSIS CKD PATIENTS: A COMPARISON BETWEEN A HOSPITAL IN MALAYSIA AND SAUDI ARABIA

ABSTRACT

Chronic Kidney Disease (CKD) is a global health concern which constitutes a considerable share of the diseases burden around the world. For controlling the progress of CKD, many strategies have been proposed. However, there are still many questions to be answered in this segment of clinical practice especially in countries like the Kingdom of Saudi Arabia (KSA) and Malaysia. For instance, the use of statins for CKD patients is still controversial due to contradictory evidence. Also, the Health-Related Quality of Life (HRQOL) of non-dialysis CKD patients has not been assessed in the formerly mentioned countries. Furthermore, the Knowledge Attitudes and Perceptions (KAPs) of Healthcare Professionals (HCPs) in Malaysia and KSA have not been evaluated even though HCPs especially nephrologists are the mainstay of the appropriate CKD guidelines implementation. Therefore, the aims of this study are to investigate the renoprotective effect and complications of different doses/types of statins (arm A of the study), to evaluate the health-related quality of life of Malaysian and Saudi ND-CKD patients (arm B), and to assess pharmacists and physicians knowledge and awareness about using statin in CKD patients in the Malaysian and the Saudi hospitals and healthcare settings (arm C). For arm A (statin use), 455 patients from Hospital Pulau Pinang (HPP), Penang, Malaysia, and 431 patients from Security Forces Hospital Program (SFHP) in Riyadh, KSA who were taking statins (different types and doses) and satisfied the inclusion and the exclusion criteria of the study were included. The observational prospective study design was adopted where the study

participants were followed on the baseline, three, six, and nine months intervals. Only atorvastatin 40 mg showed significantly higher potassium and significantly lower urea level than placebo. Furthermore, there was no significant difference in the impact of Simvastatin 20mg when used in Malaysian and Saudi population. For arm B (HRQOL), A total of 526 non-dialysis CKD Malaysian patients and 301 Saudi patients were included to fill out the SF-36 validated questionnaire. A cross-sectional research design was used to assess the effect of CKD on HRQOL scores among non-dialysis CKD patients at HPP in Penang, Malaysia, and the SFHP in Riyadh, KSA. Young age, lower CKD duration and stage, higher income, and higher educational level were all associated with higher HRQOL scores. In conclusion, these observations highlight the strong impact of ND-CKD on HRQOL. Further studies to design and evaluate potential interventions for improvement of HRQOL in ND-CKD patients are warranted. For arm C (KAPs), A cross-sectional design was employed using a self-administered questionnaire that was constructed and validated before the study. The questionnaire was distributed to 187 HCPs at SFHP in Riyadh, Saudi Arabia, and 122 HCPs at HPP in Penang, Malaysia. Medical journals were chosen as the fundamental source for updated CKD information in both Malaysia and KSA (30% and 39% respectively). More than 90% of them agreed with the necessity of early referral of CKD patients to a nephrologist. Older age, specialist physicians, longer experiences, highest salaries were consistently related to higher scores. Lastly, there is room for improvement of CME programs, and HCPs knowledge regarding CKD and the use of statins. HCPs from both countries hold a positive attitude/Perceptions towards statins use in improving CKD patients' outcomes.

CHAPTER ONE

INTRODUCTION

1.1 General Introduction

Chronic kidney disease (CKD) is a major public health problem (James et al., 2010). Cardiovascular disease (CVD) continues to be the leading cause of morbidity and mortality among people with CKD worldwide, with rates of cardiovascular events and mortality consistently increasing as kidney function declines (Friel, 2014, Go et al., 2004). Dialysis patients have mortality rates up to 40-fold higher than the general population, with CVD being responsible for up to 50% of these deaths (Sarnak, 2000).

Patients with CKD have a higher prevalence of a number of risk factors for CVD, including lipid abnormalities, hypertension, obesity, and diabetes. Kidney Disease Outcome Quality Initiative (K/DOQI) clinical practice guidelines have recommended statin therapy for the prevention of CVD in patients with CKD and high-low density lipoprotein cholesterol (LDL-C) levels (Snyder, 2009). However, the value of this approach continues to be debated, particularly in those with the most advanced kidney dysfunction. Levels of cholesterol in patients with kidney disease do not always have the same log-linear relationship with cardiovascular events observed in the general population (Liu, 2004).

The burden of CVD may not be predominantly due to atherosclerotic disease in people with severely decreased GFR when compared with people with normal renal function. Emerging data suggest the pattern of cardiovascular pathology may be different in advanced CKD, with vascular stiffness and calcification, structural heart disease, and sympathetic overactivity contributing to an increased risk of cardiac arrhythmia and heart failure (Foley, 1998).

1.2 Chronic Kidney Disease (CKD) Definitions

Kidney disease can either be acute or chronic. In acute kidney injury (AKI), there is a reversible decline in kidney function, whereas chronic kidney disease (CKD) is the progressive destruction of kidney mass through loss of nephrons and irreversible sclerosis over a period of months or years (Venkatachalam, 2010, López-Novoa, 2010).

CKD can also lead to end-stage renal disease (ESRD), due to which the patients normally require dialysis and renal transplantation. Both dialysis and renal transplantation are termed as renal replacement therapy (RRT). RRT has a considerable effect on the patient quality of life (QoL) as well as survival (Bellomo, 2004).

CKD is defined as abnormalities of kidney structure or function, present for 3 months, with implications for health (Xie et al, 2017). The definition of CKD remains intact. The addition of ‘with implications on health’ is intended to reflect the notion that a variety of abnormalities of kidney structure or function

may exist, but not all have implications for the health of individuals, and therefore need to be contextualized. Kidney damage refers to a broad range of abnormalities observed during the clinical assessment, which may be insensitive and non-specific for the cause of disease but may precede reduction in kidney function. Excretory, endocrine and metabolic functions decline together in most CKD patients. Glomular Filtration Rate (GFR) is generally accepted as the best overall index of kidney function. It is known that a GFR 60 ml/min/ 1.73m2 as decreased GFR and a GFR 15 ml/min/ 1.73m2 as kidney failure (Matsushita et al., 2012).

1.3 Global Burden of Chronic Kidney Disease

Chronic kidney disease is a major problem with a worldwide prevalence that varies from country to country ((Vos, 2015). The median prevalence of CKD in individuals aged ≥ 30 years old was 7.2%, while its prevalence in persons aged ≥ 64 years old ranged from 23.4-35.8% (Mula-Abed, 2012). In the U.S., the prevalence of stage 5 CKD (kidney failure or hemodialysis) is 0.1% of the U.S. population and the prevalence of mild to severe disease (CKD stages 1 to 4) is 11% of the U.S. population (Pitt, 1999, Harper, 2010). Chronic dialysis is annually associated with mortality rate approximately up to 20% (Go, 2004)

CKD is also a devastating socio-economic problem across the world. The global annual growth rate of CKD is 8%, while annual dialysis growth rates are 6-8% per annum. Disease of the genitourinary system is the 12^{th} and 17^{th} cause of mortality and disability worldwide respectively (Allon, 2011).

The lifetime of chronic kidney failure is one among fifty during the age of 40 years (Huang, 2006). The global burden of disease study in 2010 reported that CKD stands 27th among the global list of total death causes in 1990 but in 2010 it becomes increased and ranked 18th (annual death rate 16.3 per 100 000) (Garrido, 2015). Chronic kidney failure enlisted 5th as the most common reason of death in some developing countries like South America (Colombia, Costa Rica, El Salvador, Mexico, and Venezuela), Andean (Bolivia, Ecuador, and Peru) and Latin America (Moncayo, 2017).

1.4 Treatment/ Prevention of chronic kidney disease

Proper management can possibly decrease the advancement of CKD and also decrease the risk of mortality due to CVD. The most important is to control the blood pressure of CKD patients with drugs which block the renin-angiotensin pathway, and control blood glucose level (James, 2014). The lipid level will decrease in CKD patients as a result of treating hyperlipidemia, which will further reduce the chances of atherosclerosis and CVD in CKD patients (Sarnak, 2003). Most suitable and easy tool is maintaining a normal level of protein and salt (James, 2014). CKD can be controlled by various approaches which include blood-pressure control, adherence to treatment, glycemic control, information about the disease, dietary habits, and lifestyle by self-management and health-related professionals (Von, 1997). In order to treat CKD patients, a multidisciplinary approach should be followed to get better outcomes (James, 2014).

1.5 Statins and Chronic Kidney Disease

In the general population, beneficial effects of statin treatment on cardiovascular endpoints are well established (Ridker, 2008). Chronic kidney disease (CKD) is a status of specific lipid disturbances, dyslipidemia with increased levels of triglycerides (TG), small dense and oxidized LDL (oxLDL), and lower high-density lipoprotein (HDL) cholesterol levels. In nephrotic syndrome, also total cholesterol and LDL levels are elevated (Agarwal, 2007). As patients with CKD and albuminuria have an increased incidence of cardiovascular disease, they should be considered for statin therapy. However, currently, only 25% of CKD patients are under continuous statin therapy. The indirect and direct effects of lipids on glomerular structure have been described in detail in animal models of renal damage (Kasiske et al., 1990) as well as in human subjects (Keane et al., 1990). Therefore, in theory, beneficial systemic and renal effects of lipid-lowering in CKD by statins could be expected. In fact, there are indeed well-proven general effects of statins in CKD patients, lipid-lowering, anti-inflammatory and anti-oxidative effects (Campese, 2007).

The relative decrease in cardiovascular risk by statins diminishes in magnitude as kidney function declines, even after allowing for the smaller reductions in LDL cholesterol obtained in more advanced CKD. In patients on maintenance dialysis, several large randomized trials and high-quality meta-analyses revealed that statins have little or no effect on cardiovascular outcome, despite significant LDL cholesterol lowering (Herrington, W., et al, 2016). These

counterintuitive findings have been attributed to the poor association of LDL cholesterol with cardiovascular risk in the dialysis population, owing to the predomination of nontraditional risk factors (e.g., mineral and bone metabolism disorder and oxidative stress) and nonatherosclerotic cardiac events (e.g., arrhythmia and heart failure) drowning out classic atherosclerotic disease (Kassimatis, T.I., et al, 2014). Chronic kidney disease is characterised by either reduced glomerular filtration rate (GFR) or significant proteinuria. This is associated with increased cardiovascular mortality, which becomes more than 10-fold greater in those on dialysis compared with the general population (Herzog, C.A., et al, 2011). Renal transplantation lowers this risk, but cardiovascular disease remains the leading cause of death for transplant patients (Israni, A.K., et al, 2010).

A characteristic pattern of lipid abnormalities affects those with chronic kidney disease (Keane, W.F., et al, 2012) and is implicated in the high rates of cardiovascular morbidity and mortality in this population (de Jager, D.J., et al,2009). Traditional cardiovascular risk factors such as diabetes and hypertension also contribute. These are prevalent in the chronic kidney disease population along with the proposed cardiovascular risk associated with oxidative stress, inflammation, insulin resistance, anaemia and disturbances of mineral metabolism.

Although statins reduce cardiovascular disease in those at increased risk, (Cannon, C.P., et al, 2015) their effect is less clear in people with chronic kidney disease as most lipid-lowering trials exclude these patients or focus on those receiving haemodialysis.

Few studies have looked specifically at lipid-lowering therapy in patients with chronic kidney disease. Most evidence is derived from subgroup or post hoc analyses.

Patients not on dialysis

A meta-analysis of statin efficacy in non-dialysis chronic kidney disease stages 1–5 reported an overall decreased risk for cardiovascular mortality and non-lethal cardiovascular events. Statins resulted in a RR* of 0.72 (95% CI† 0.66–0.79) for major cardiovascular events, 0.55 (95% CI 0.42–0.72) for myocardial infarction, 0.79 (95% CI 0.69–0.91) for all-cause mortality and an uncertain effect on stroke (RR 0.62, 95% CI 0.35–1.12). Adverse events with statins included elevated creatinine kinase and liver function abnormalities. There was no evidence of an effect on renal function (Athyros, V.G., et al, 2015).

The benefit of statins appears to diminish with progression of chronic kidney disease. This probably contributes to the inconsistent relationship in studies between cholesterol-lowering therapy and cardiovascular outcome in chronic kidney disease (Zhang, X., et al, 2014). In a more recent meta-analysis, statin therapy reduced the risk of first major vascular event by 21% (RR 0.79, 95% CI 0.77–0.81) per mmol/L reduction in LDL cholesterol. Smaller relative effects on major vascular events, major coronary events and vascular mortality were observed as GFR declined (Trialists, C.T., 2016).

The SHARP trial, (Baigent, C., et al, 2011) which enrolled patients with pre-dialysis chronic kidney disease and those on dialysis, evaluated daily simvastatin 20 mg plus ezetimibe 10 mg or placebo. In the pre-dialysis cohort of 6247 patients (mean GFR of 26.6 mL/min/1.73 m2), LDL cholesterol fell by 0.85 mmol/L over five years. These patients had a 17% RR reduction in major atherosclerotic events (RR 0.83, 95% CI 0.74–0.94) compared with placebo and the number needed to treat was 48. This compares favourably with numbers needed to treat in primary prevention studies of statins in the general population (Downs, J.R., et al,1998). There was a significant reduction in non-haemorrhagic stroke (RR 0.75, 95% CI 0.60–0.94) and in arterial revascularisation procedures (RR 0.79, 95% CI 0.68–0.93), but no effect on progression of chronic kidney disease (Haynes, R., et al, 2014).

The rate of adverse events in the SHARP trial was low – myopathy was reported in 0.02% of patients and there was no evidence of increased hepatitis, gallstones, pancreatitis or malignancy in the lipid-lowering group. While this is the largest trial of lipid-lowering drugs in patients with chronic kidney disease to date, it failed to evaluate the role of a statin or ezetimibe alone. Other trials of lipid-lowering therapy in non-dialysis chronic kidney disease show considerable heterogeneity both in study design and impact on cardiovascular end points.

Patients on dialysis

In addition to the SHARP trial, (Baigent, C., et al, 2011) there have been two major placebo-controlled randomised trials of statin therapy in haemodialysis patients – 4D (Wanner, C., et al, 2005) and AURORA (Fellström, B.C., et al, 2009) . The 4D study evaluated the effect of 20 mg atorvastatin on cardiovascular disease and death. It included only patients with diabetes and a high cardiovascular disease burden. Despite a profound reduction of LDL cholesterol early in the trial, there was no significant impact on major cardiovascular events or all-cause mortality. A higher rate of haemorrhagic stroke was observed in the atorvastatin group. Post hoc analysis revealed that atorvastatin was beneficial with respect to cardiac events and all-cause mortality in patients with a high baseline LDL (März, W., et al, 2011).

AURORA investigated the effect of rosuvastatin in haemodialysis patients and likewise found no significant impact on major cardiovascular events (Fellström, B.C., et al, 2009). The study also reported an increased incidence of fatal haemorrhagic stroke with rosuvastatin in patients with diabetes, reinforcing the adverse outcomes noted in the 4D study. While the SHARP trial reported a reduction in major atherosclerotic events in the study population overall, a subgroup analysis of those on dialysis revealed no benefit (RR 0.9, 95% CI 0.75–1.08) (Baigent, C., et al, 2011) .

A recent meta-analysis conducted by the Cholesterol Treatment Trialists' Collaboration indicated there was no benefit in terms of major vascular events, major coronary events or vascular mortality to support statin use in dialysis patients (Haynes, R., et al, 2014).

Statin therapy appears to offer some benefit in patients with renal disease who are not on dialysis and to a more limited extent after transplant. There is no evidence to support commencing statins in that receiving dialysis. Evidence supports the safety of statins in chronic kidney disease, but caution is advised with high doses and when there is a potential for drug–drug interactions.

1.6 Chronic Kidney Disease in Malaysia and Saudi Arabia

The Malaysian dialysis registry has demonstrated the rapid growth of dialysis provision in this country. This has been particularly dramatic in the older age groups. It has also shown that diabetic nephropathy leading to ESRD is on the rise and accounts for more than 50% of all incident dialysis patients. Hence prevention of ESRD is eminently achievable with better management of diabetes mellitus (Lim et al, 2008). On the other hand, Singapore aimed to assess the prevalence and risk factors of CKD in a multi-ethnic Asian population. They studied 4499 participants, aged 24-95 years. The age, sex-standardized prevalence of CKD was 12.8% (11.4%, 18.6% and 17.6% in Chinese, Malays, and Indians respectively). Older age and the presence of diabetes, hypertension, and dyslipidemia were significantly associated with CKD in all ethnic groups. Diabetes (45%) and dyslipidemia (16%) among Malays and hypertension among

Indians (23%) had a greater population- attributable risk of CKD (Villa-Zapata et al, 2016).

As the world's population ages and the diabetes epidemic continues unabated, chronic kidney disease (CKD) is emerging as an important non-communicable disease worldwide (Levey et al, 2007). The three very important risk factors for CKD – diabetes, hypertension, and obesity– are highly prevalent in the Arab world, more so than perhaps anywhere else (Hooi et al, 2013).

Progression of CKD to end-stage renal failure (ESRF) has tremendous human and economic implications. Mortality is as much as 17-fold higher in patients with ESRF compared to age- and gender-matched healthy individuals and the cost of dialysis or transplantation is frequently unaffordable to many in the absence of governmental programs (Hassanien et al, 2012).

Data available on the exact prevalence of various kidney diseases in the Arab world is very limited. Reviewing the recent literature illustrated that there is no Arab country with up-to-date information on the epidemiology of CKD. Most of the data come from small studies of approximately 100 patients or less. Based on their size and other design considerations, data from these studies have limited generalizability (Farag et al, 2012). Prevalence (95% confidence interval (CI)) of all stages CKD was 9.4%. In Hail, Saudi Arabia (Ahmed et al, 2014), while the overall prevalence of CKD was 5.7% in Riyadh, Saudi Arabia (Alsuwaida et al, 2010). There is a lack of accurate data on the CKD prevalence (Ahmed et al, 2014).

1.7 Problem Statement

There is a shortage in previous studies that have evaluated the renoprotective impact of statins and their risk factors and complication in CKD patients in Malaysia and Saudi Arabia, also there are limitations in previous studies that evaluate the quality of life of CKD patients and that assess the knowledge of healthcare team professionals about using of statins among CKD patients. The relation between the renal protective effect of different statins and different doses of the same statin has not been reported yet.

In the past few years, several large-scale trials of statin therapy in people with CKD have been completed, including the recent large SHARP (Study of Heart and Renal Protection) trial (Baigent et al, 2011). Although some of these trials have shown benefit, (Baigent et al, 2011), others have shown no effect (Fellström et al, 2009), leading to uncertainty about the presence and magnitude of renal protective effects and therefore difficulties for clinicians in the interpretation of the results into clinical practice (Jun et al, 2010).

Two recent reviews have investigated the effect of statin in patients with CKD. However, both have not evaluated the effect of kidney function on statin therapy (Palmer et al, 2012, Upadhyay et al, 2012). No data are available on the clear effect of statin on renal outcomes in Saudi Arabia and Malaysia.

1.8 Significance of the Study

The majority of studies about the use of statins among non-dialysis CKD patients and quality of life of patients are conducted in developed countries and among the patients on dialysis, but there is limited data on statin use among CKD patients in Malaysia and Saudi Arabia. Research results on the renoprotective effect of statins among non-dialysis CKD patients and quality of life of the patients in Malaysia and Saudi Arabia could be used for better treatment and prevention of CKD progression in this population. The unique characteristics of this population could also be used for participation in global trials and a better understanding of the progression of CKD in those countries.

Limited data are available about the using of statins among non-dialysis CKD patients in Malaysia and Saudi Arabia, and there is probably no information on baseline characteristics, in-hospital outcomes, quality of life outcomes, and the renal protective outcomes of statins of the non-dialysis CKD patients. This information could assist in distinguishing between the renal protective effect of different doses or different generic types of statins among the non-dialysis CKD patients.

In addition, there are no data about the effect of CKD on the health-related quality of life of non-dialysis CKD patients in Malaysia and Saudi Arabia. These results could help to improve the quality of life of patients by finding the factors that affect the level of quality of life of those patients and create new interventions to improve it.

There is probably no information about the knowledge of healthcare team professionals about the importance and the benefit of using statins among non-dialysis CKD patients. Obtaining these data could increase the awareness about the use of statins among this population and assists in early detection and prevention of the disease progression.

To achieve the goals of this study, the three arms (aspects) of the study were integrated. First the study of the renoprotective effect of statins found the best statin to decrease CKD progression in parallel enhancing the HRQoL ,by knowing the factors that affect it,of non dialysis CKD patients would decrease CKD progression also. Early referral of CKD patients to nephrologists would also decrease CKD progression this information would be collected from KAP survey (Figure 1.1).

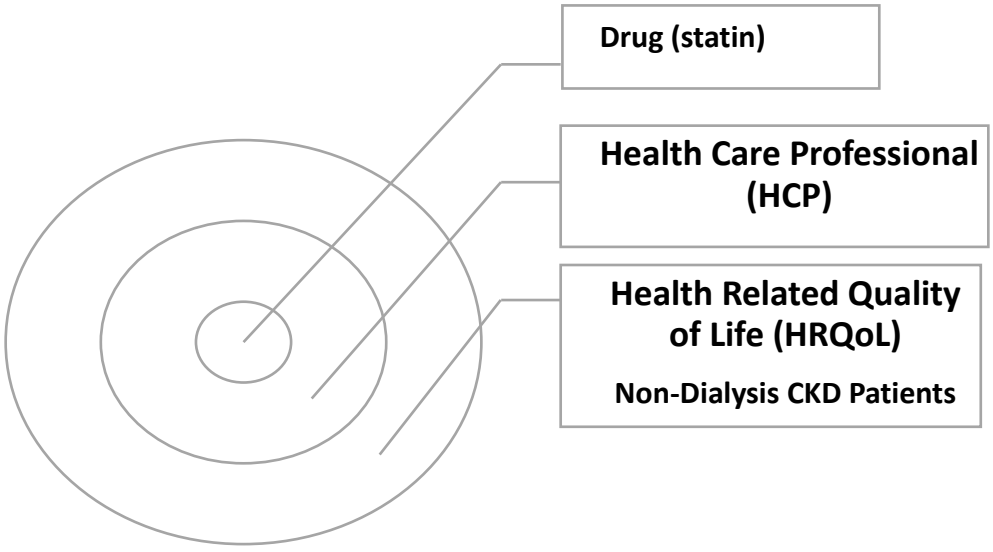

Figure 1.1: General Aspects of Study

1.9 Study Objectives (figure 1.2)

1.9.1 General Objectives

1. To determine and compare the relationship between statin use and the progression of renal dysfunction among non-dialysis CKD patients receiving statins in Saudi Arabia and Malaysia.
2. To evaluate the quality of life of non-dialysis CKD patients who used statins in Malaysia and Saudi Arabia.
3. To assess pharmacist and physician knowledge, attitude and perception about the use of statin in non-dialysis CKD in Malaysia and Saudi Arabia.

1.9.2 Specific Objectives

1. To investigate the risk factors and complications of statins use among non-dialysis CKD patients.
2. To compare the Reno-protective effect of different doses of Atorvastatin in KSA and Simvastatin in Malaysia among non-dialysis CKD patients.

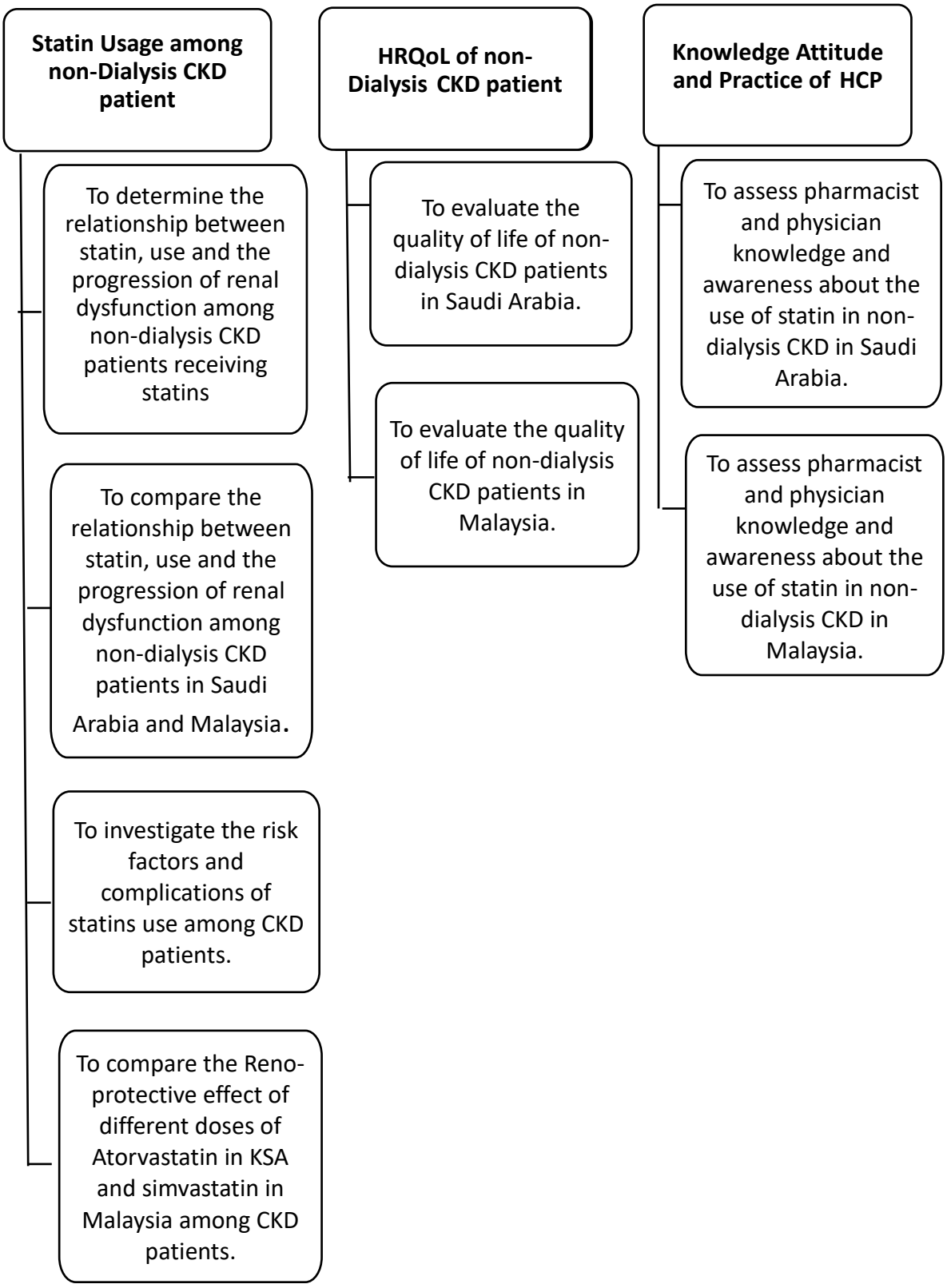

Figure 1.2: Study Objectives

1.10 The Framework of Thesis

To meet the objectives of this thesis, assessment of the renal protective effect of statin use among non- dialysis CKD patients, health-related quality of life and knowledge, attitude and perception of healthcare professionals about the use of statins among non-dialysis CKD patients have been narrated in this thesis (Figure 1.3).

The **first chapter** is an orientation chapter in which background about CKD was introduced. This section sketches the global burden of chronic kidney disease and the relation between statins and chronic kidney disease. The significance of the study, statement of the problem was presented. Following that, the objectives of the current study are formulated and presented. Lastly, the visual presentation on the current study's organization was provided.

Statins and clinical outcomes of non-dialysis CKD:

The **second chapter** comprises a review of the literature related to the current study. This contains a review of the research paradigm. Next, an overview of the major issues related to CKD is provided. Of importance, this section also presented the statins effect on cardiovascular and renal outcomes. The clinical characteristics of in-hospital outcomes and pharmacology treatment of non-dialysis CKD shown in this chapter. Also, a comprehensive discussion of the data collection procedures and strategies were illustrated. Then the results of the research hypothesis have been mentioned and the answers achieved through several research analysis procedures.

Patient health-related quality of life and non-dialysis CKD:

The **third chapter,** A research review of health-related quality of life issues was discussed and illustrated as well. It also is concerned with the methodology employed in this research. The research design employed in this study was described. Further, as this research aims to understand the effect of health-related quality of life among non-dialysis CKD patients, a comprehensive discussion of the data collection procedures and strategies is illustrated.

A section on pilot testing the instruments that were used in the study were illustrated. It also explains the sample size and population under the study. The experimental procedures that were carried out are explained as well. This chapter offers a discussion on the measurement tools utilized in this research as well. Particularly, the construction, validity, and reliability of measurement tools carried out in this research are also discussed. the statistical analysis procedures are discussed in this chapter. Finally, Each objective and its levels were presented in separate sections and statistical analysis employed is explained in each section.

Knowledge, attitude and practice of health care professionals and statin use among non- dialysis CKD patients

The **fourth chapter** A research review of KAP issues was discussed and illustrated as well. It also is concerned with the methodology employed in this research. The research design employed in this study is described. Further, as this research aims to understand the effect of Knowledge, attitude and practice of health care professionals and statin use among non-dialysis CKD patients, a

comprehensive discussion of the data collection procedures and strategies are illustrated.

A section on pilot testing the instruments that were used in the study was illustrated. It also explains the sample size and population under the study. The experimental procedures that are carried out are explained as well. This chapter offers a discussion on the measurement tools utilized in this research as well. Particularly, the construction, validity, and reliability of measurement tools carried out in this research and the statistical analysis procedures were discussed in this chapter. Finally, each objective and its levels were presented in separate sections and statistical analysis employed is explained in each section.

The **fifth chapter** presents the major conclusions and implications of the study. These conclusions and implications were important to know what the most important results were achieved and, importantly, drawn upon them a solid understanding of guidelines implementation and how functionally statins are operating in CKD context, the non-dialysis patients one in specific

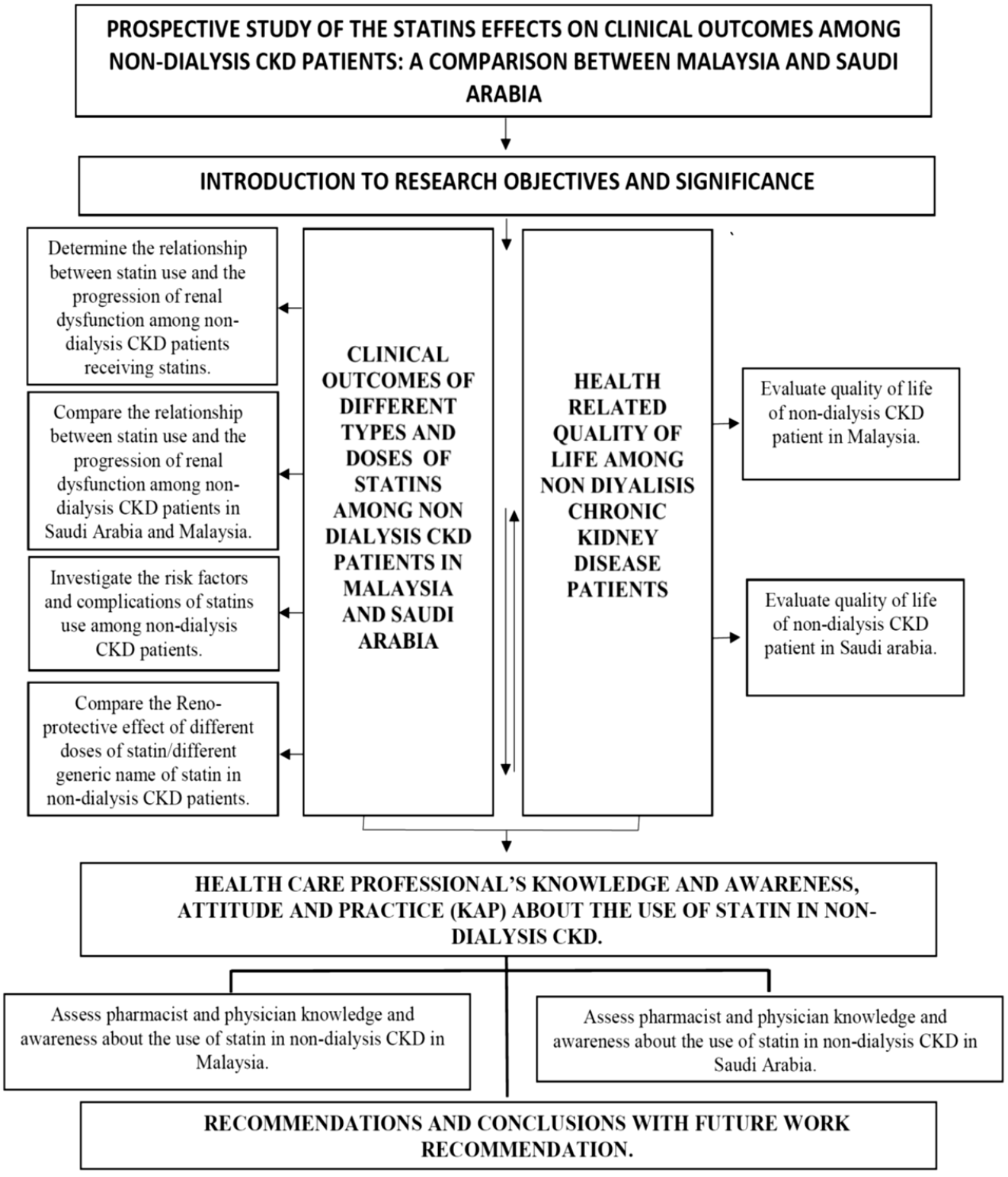

Figure 1.3: Framework of Thesis

CHAPTER TWO

CLINICAL OUTCOMES OF DIFFERENT TYPES AND DOSES OF STATINS AMONG NON DIALYSIS CKD PATIENTS IN MALAYSIA AND SAUDI ARABIA

2.1 Introduction

2.1.1 Background

CKD is a major health problem across the globe (Schieppati, et al.,2005) and attention paid towards CKD is attributable to five factors, escalating prevalence, enormous treatment cost, recent data tell-tale problem that overt disease (stage 3 to 5) is merely the tip of iceberg of furtive disease (stage 1 to 2), its major involvement in increasing risk of cardiovascular events and discovery of effective measures to retard its progression (Sturm, 2002).

CKD is a pathological condition which affects the morphology and efficiency of kidneys. The variation in disease expression is somehow related to various factors like cause, pathology, severity and also on the rate of progression (Petrosyan et al.,2016). CKD in the last 12 years has changed from life-threatening to common manageable disorder (Jin, et al., 2016). The development of CKD model, better guideline for definition and staging of CKD has aided in early detection and even in the prevention of CKD (Peralta et al.,2011, Klahr et al.,1994, Cunningham et al.,2011).

2.1.2 Statins

2.1.2(a) Dyslipidemia

Dyslipidemia is a major risk factor for cardiovascular morbidity and mortality and is common among patients with CKD. Lipid profiles vary widely in these patients, reflecting the level of kidney function and the degree of proteinuria (Holdaas et al., 2005). In general, the prevalence of hyperlipidemia increases as renal function declines, with the degree of hypertriglyceridemia and elevation of LDL cholesterol being proportional to the severity of renal impairment.

Several factors contribute to the development dyslipidemia associated with chronic renal impairment. Patients with CKD have a reduction in the activity of lipoprotein lipase and hepatic triglyceride lipase. This interferes with uptake of triglyceride-rich, apolipoprotein B containing lipoproteins by the liver and in peripheral tissue, yielding increased circulation of these atherogenic lipoproteins. Hypercholesterolemia in nephrotic syndrome is thought to be due to increased production and decreased catabolism of lipoproteins. The degree of lipoprotein abnormality is roughly proportional to the amount of proteinuria and inversely proportional to serum albumin levels. However, infusions of albumin or dextran both normalize lipoprotein concentrations, suggesting that oncotic pressure changes rather than hypoalbuminemia signals increased lipoprotein synthesis by the liver. Additional data supporting this hypothesis is derived from in-vitro experiments demonstrating direct stimulation of increased hepatic apolipoprotein-B gene transcription in cells exposed to reduced oncotic pressure

(Yamauchi et al., 1992). Studies also suggest that hyperparathyroidism and the accumulation of calcium in pancreatic islet cells likely contribute to dyslipidemia of CKD as well (Arnadottir et al., 1995).

Clinical trials in the general population have demonstrated that coronary heart disease mortality decreases proportional to LDL-cholesterol level reduction. Evidence for benefit of statins in reducing cardiovascular risk (i.e., composite outcomes) in CKD patients is less definitive. Recently, the largest clinical trial of statins in patients with stage 5 CKD (4D trial) was conducted in Germany, In this study, atorvastatin did not to reduce death from fatal stroke, nonfatal myocardial infarction, or nonfatal stroke in 200 patients with diabetes and stage 5 CKD (Wanner et al., 2005). The results of the Study of Heart and Renal Protection (SHARP) provide further insight into the role of cholesterol lowering therapy in reducing cardiovascular events in kidney disease patients. SHARP is a prospective, randomized trial in which 9,000 patients with CKD and 3,000 dialysis patients without coronary artery disease have been enrolled to assess the effects of lowering LDL-cholesterol with the combination of simvastatin and ezetimibe, with the primary outcome measure being the time to a first "major vascular event" defined as non-fatal myocardial infarction or cardiac death, non-fatal or fatal stroke, or an arterial revascularization procedure. The SHARP results show that lowering LDL cholesterol with the combination of simvastatin plus ezetimibe safely reduces the risk of major atherosclerotic events in a wide range of patients with chronic kidney disease. As in people without

kidney disease, the proportional reduction in major atherosclerotic events produced by a given absolute reduction in LDL cholesterol is broadly similar irrespective of age, sex, diabetes, history of vascular disease, and presenting lipid profile. The SHARP results are relevant, therefore, to most patients with chronic kidney disease, SHARP did not have sufficient power to assess the effects on major atherosclerotic events separately in dialysis and non-dialysis patients, but there was not good statistical evidence that the proportional effects in dialysis patients differed to those seen in patients not on dialysis. Moreover, since about a third of the patients who were not on dialysis at baseline began dialysis during the trial (with about one third of those doing so within the first year), the effects of simvastatin plus ezetimibe in the dialysis subgroup are reinforced by the favourable results in the non-dialysis subgroup.

A relationship between total cholesterol levels and coronary heart disease (CHD) mortality as the primary outcome also has not been clearly established. In fact, several observational studies of stage 5 kidney disease patients suggest that lower total cholesterol levels are associated with higher mortality rate. For example, in a recent 10 -year prospective study the importance of total cholesterol levels on mortality was evaluated in 1,167 stage 5 kidney disease patients (Higashiuesato et al., 2002). Hypercholesterolemia (total cholesterol levels >200) was associated with increased all-cause mortality rate. Scintists suggests that decreased cholesterol and low cholesterol levels may be an indicator for poor health status. The clinical implication of the study was that individuals with spontaneously decreased cholesterol or persistently low cholesterol levels are at