Development of Cardiovascular Risk Assessment Model for People with Type 2 Diabetes in Oman

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Incidence, risk factors, cardiovascular disease, coronary heart disease, stroke, peripheral arterial disease, type 2 diabetes mellitus, CVD risk, prediction model, risk equation, validation, performance, Arab, Oman

Abstract

Type 2 diabetes mellitus (DM) is one of the most common chronic diseases globally, with worldwide prevalence of 8.3%. Due to its long-lasting nature and high risk of complications, the burden of type 2 DM is expected to rise. Patients with type 2 DM have an estimated two-to-six fold higher risk of developing cardiovascular disease (CVD) compared to the general population. Moreover, CVD is considered the leading cause of morbidity and premature mortality in type 2 diabetic patients.

CVD risk assessment tools in general are mathematical models or charts used to estimate the risk of a CVD event in an individual. CVD risk estimation is important to plan the initiation of preventive and therapeutic measures for CVD prevention including anti-lipid, anti-hypertensive and anti-platelet therapies, as well as to plan appropriate health education. Various professional guidelines for the management of type 2 DM have advocated the use of CVD risk assessment tools to estimate CVD risk among type 2 diabetic patients using traditional CVD risk factors such as hypertension (HTN), dyslipidemia, high glycosylated hemoglobin (HbA1c), albuminuria, obesity, smoking status, and family history of CVD. However, most of the existing CVD risk assessment tools were derived from Western populations, with very few developed for East Asian populations.

In Oman, as in other Arabian Gulf countries, type 2 DM represents a high public health burden. Related data in Oman have shown a gradual increase in the prevalence of DM from 10% in 1991 to 12.3% in 2008. As for CVD, local data collected from the Omani general population indicate that CVD accounted for 29.8% of total causes of death in 2013 according to the Ministry of Health. However, there is very limited literature available related to CVD occurrence and the distribution of its risk factors among Omani type 2 diabetic patients. As for CVD risk assessment models used in prevention and management of CVD among diabetics, no CVD risk assessment tool has yet been developed for any Arabian population, including Omanis. Despite the availability of international risk assessment tools, these are not considered optimal for Omani diabetics. As populations differ in many ways such as

differences in lifestyle patterns, socio-demographic characteristics and trends in the incidence of diabetes and CVD risk factors, the existing international CVD risk assessment models are not suitable for Omani or even Arabian diabetic populations. Hence, the overall aim of this project was to develop a risk assessment tool that is suitable to estimate the 5-year CVD risk among Omanis with type 2 diabetes.

To achieve the main aim of this research project, three subsequent studies were conducted. The objective of the first study was to assess the incidence of CVD and the patterns of traditional CVD risk factors among Omani type 2 diabetics. A retrospective cohort study was undertaken on a sample of 2,039 patients with type 2 DM selected from four primary healthcare institutions in Aldakhiliyah Governorate (Province), all of whom were free of CVD at baseline in 2009 – 2010. Socio-demographic and baseline data regarding traditional risk factors were retrieved from the patients' medical records. The CVD outcome was defined as the first confirmed diagnoses of coronary heart disease (CHD), stroke or peripheral arterial disease (PAD) during the study period, up until December 2015, with a mean and median follow-up period of 5.3 and 5.6 years respectively.

This study revealed an overall cumulative CVD incidence of 9.4% among Omani diabetic patients, with an incidence density of 17.6 cases per 1,000 person-years. A high prevalence of most CVD risk factors was observed among the study sample. For example, the prevalence of poor glycemic control (as indicated by a high level of HbA1c), HTN, obesity, dyslipidemia, and albuminuria was 40%, 56.3%, 39%, 77.3% and 18.7% respectively. A univariate survival analysis showed a significant association between CVD and the following factors: age; DM duration; body mass index (BMI); glycemic control; HTN; total serum cholesterol and albuminuria (P value < 0.05 each). In addition, compared to similar global studies, important differences in the prevalence of some risk factors and their patterns in the univariate associations with CVD outcome were observed.

The second study aimed to develop a suitable CVD risk prediction tool for Omanis with type 2 diabetes, in consideration of the specific patterns of CVD

risk factors in this population. This study was conducted based on the same study sample used in the first study. However, patients with incomplete data related to any key risk factor were excluded in the derivation of the model using a Cox regression analysis. As such, a total sample of 1,314 patients with complete data was used to develop the model. All included patients were free of CVD at baseline (2009-2010) and were followed up until any of the following end-point events occurred: their first CVD event (either CHD, stroke, or PAD), death, or the end of the follow-up period in December 2015. All data were retrieved from the diabetes registry and the patients' computerised files at the primary care settings.

Among the study sample, 192 CVD events were recorded within a mean follow-up period of 5.3 years. This study modelled the 5-year probability of CVD as: $1 - 0.9991^{Exp\sum XiBi}$, where $Exp \sum XiBi$ (which represents the hazard ratio) = *Exp* (0.038 age [years] + 0.052 DM duration [years] + 0.102 HbA1c [%] + 0.201 total cholesterol [mmol/l] + 0.912 albuminuria [coded 1 if present] + 0.166 HTN [coded 1 if present] + 0.005 BMI [kg/m^2])

The aim of the third study was to validate the model developed in the second study. The performance of the model was assessed in two samples: the derivation sample used to develop the model, which consisted of the 1,314 diabetics described previously, and another separate validation sample selected from two institutions in the same region. This validation sample included 405 type 2 diabetics which were not included in the model derivation. All patients were free of CVD at baseline (2009-2010). All of the end-point events for the validation sample were defined as for the derivation sample. All data were retrieved from the patients' medical records. This study showed adequate model discrimination in both the derivation and validation samples, with an area under the receiver operating curve of 0.73 (95% confidence interval [CI]; 0.69 – 0.77) and 0.70 (95% CI: 0.59 – 0.75) respectively. The calibration of the model also showed acceptable results, with insignificant differences between the mean predicted risks (estimated by the model) and the actual mean risks, with differences ranging from 0.7% - 3.1% and 0.1% - 4.2% (*P* value > 0.05 each) in the derivation and validation samples

respectively. In addition, the recommended optimal CVD risk cut-off point was 10.0%, yielding good sensitivity (73.0%) and reasonable specificity (60.3%).

This research project revealed the limited applicability of existing international CVD risk assessment tools in Oman, and the need to develop a specific tool suitable to estimate CVD risk among Omani type 2 diabetic patients. Subsequently, a CVD risk assessment model for people with type 2 diabetes in Oman was developed in view of the specific risk factor profile of this population. The model was validated in both the study sample and an external sample, and was shown to be suitable for the Omani type 2 diabetic population. Therefore, the present model is considered a suitable tool to estimate CVD risk at least for type 2 diabetic patients in Aldakhilyah Province, in order to plan their clinical management strategies and CVD prevention measures. In addition, health planners may use this model to monitor CVD risk and estimate the future burden of CVD among Omani diabetics. However, the wider generalisability of this model requires further validation studies in different provinces of Oman, as well in neighboring Gulf countries. Nevertheless, the use of the present model in clinical settings would allow further validation of the model over time and enable researchers to assess the cost-effectiveness of utilising this model among Omanis with type 2 diabetes.

Declaration of Originality

I (the candidate) declare here that this work has not previously been submitted for a degree or diploma in any university. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

(Signed) _____

Date: 18/04/2017

Candidate: Abdul Hakeem Hamood Al Rawahi

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List of Abbreviations

ABPI	Ankle Brachial Pressure Index
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation
ARIC	Atherosclerosis Risk in Communities
ASSIGN	Assessing Cardiovascular Risk Using SIGN Guidelines
BP	Blood Pressure
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
CT	Computed Tomography
CVD	Cardiovascular Disease
DARTS	Diabetes Audit and Research in Tayside, Scotland
DBP	Diastolic Blood Pressure
DCS	Diabetes Cohort Study
DBP	Diastolic blood pressure
DM	Diabetes Mellitus
ECG	Electrocardiogram
FDS	Fremantle Diabetes Study
FHS	Framingham Heart Study
GF	General Framingham
HbA1c	Glycosylated Hemoglobin
HDL-C	High Density Lipoprotein Cholesterol
HR	Hazard Ratio
IDF	International Diabetes Federation
IFG	Impaired Fasting Glucose
IGT	Impaired Glucose Tolerance
ISH	International Society of Hypertension
LDL-C	Low Density Lipoprotein Cholesterol
MENA	Middle East and North Africa
MRI	Magnetic Resonance Imaging
OR	Odds Ratio

PAD	Peripheral Arterial Disease
PI	Principle Investigator
PROCAM	Prospective Cardiovascular Munster study
QRISK	Cardiovascular Disease Risk Score Based on the British QRESEARCH Database
SBP	Systolic Blood Pressure
SD	Standard Deviation
SNDR	Swedish National Diabetes Register
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
U.K	United kingdom
UKPDS	United kingdom Prospective Diabetes Study
U.S	United States
WHO	World Health Organization

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Acknowledgement of published and unpublished papers included in this thesis

Included in this thesis are two papers published in a peer-reviewed journal and two manuscripts submitted for publication, in *Chapters 2, 4, 5 and 6*, which are co-authored with other researchers. The bibliographic details for these papers are as follows:

Chapter 2 (section 2.7): Al-Rawahi A, Lee P. Applicability of the Existing CVD Risk Assessment Tools to Type II Diabetics in Oman: A Review. Oman Med J. 2015 Sep;30(5):315–9. DOI: 10.5001/omj.2015.65.

Chapter 4: Al Rawahi AH, Lee P, Al Anqoudi ZAM, Al Busaidi A, Al Rabaani M, Al Mahrouqi F, et al. Cardiovascular Disease Incidence and Risk Factor Patterns among Omanis with Type 2 Diabetes: A Retrospective Cohort Study. Oman Med J. 2017;32(2):106–14. DOI: 10.5001/omj.2017.20.

Chapter 5: Al Rawahi AH, Lee P, Al Anqoudi ZAM, Al Busaidi A, Al Rabaani M, Al Mahrouqi F, et al. Cardiovascular Risk Prediction model for Omanis with Type 2 Diabetes. Manuscript submitted for publication to *'Primary Care Diabetes'* journal. 2017.

Chapter 6: Al Rawahi AH, Lee P. Validation of the cardiovascular risk model developed for Omanis with type 2 diabetes. Manuscript ready to be submitted for publication to *'Primary Care Diabetes'* journal. 2017.

Copyright of the first and second papers was transferred to the publisher, however, permission from the publisher has been obtained for the inclusion of these papers in this thesis (see appendix A).

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Chapter 1: Introduction

1.1 Background and rationale

Patients with type 2 diabetes have an elevated risk of developing cardiovascular disease (CVD), estimated as being two-to-six-fold higher compared to that of the general population.[1] CVD also represents the leading cause of morbidity and premature mortality in type 2 diabetic patients.[2]

There are many risk factors for CVD among diabetics. In fact, many traditional risk factors such as hypertension, dyslipidaemia, glycaemic control, diabetes duration, renal dysfunction, obesity, smoking and physical inactivity have been identified as independent predictors of CVD.[1,3] Other non-traditional predictors—such as erectile dysfunction, unhealthy dietary patterns and social deprivation as well as other inflammatory, haematological and thrombogenic markers—have been studied recently and have shown a positive relationship with CVD among diabetics.[1,3] However, traditional risk factors have been found to account for up to 75–90% of CVD events among people with diabetes.[4,5]

Various professional guidelines for the management of type 2 diabetes mellitus (DM) have recommended the use of CVD risk assessment tools to estimate CVD risk among diabetics and to guide the initiation of appropriate preventative and treatment strategies, including anti-hypertensive, anti-platelet and anti-lipid drugs.[6,7] In this regard, many different risk prediction tools in the form of statistical equations or risk charts have been developed in different parts of the world to estimate CVD risk among type 2 diabetics. These include tools developed for general populations which consider type 2 diabetes as a risk factor, as well as tools which have been developed specifically for type 2 diabetic populations. Examples of such tools include the Framingham Heart Study model, the Framingham General CVD (FG-CVD) Risk Profile, the new Prospective Cardiovascular Munster Score model, the World Health Organization (WHO)/International Society of Hypertension (ISH) risk prediction charts, the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation study model, the Swedish National

Diabetes Register equation and the U.K. Prospective Diabetes Study risk engine for diabetic patients.[8–10]

However, tools which were primarily derived for general populations are not specific for type 2 DM populations with higher CVD risk. Moreover, these tools do not include important traditional risk factors related to type 2 DM, such as glycaemic control, DM duration and albuminuria.[9,11] In addition, most general CVD as well as diabetes-specific tools have been derived for Western populations (primarily European and U.S. populations) and very few have been derived for East Asian populations. Among these tools, only a few have been validated externally in diabetic populations. Moreover, many of these validation studies demonstrated that the tools performed poorly when applied to different diabetic samples.[12–14] In addition, such external validation studies are usually conducted among European, Australian or other populations of similar ethnicities and lifestyles to the populations from which those tools were initially developed.

There is an increasingly high burden of type 2 diabetes in Oman. Three consecutive epidemiological surveys conducted in the country have shown a gradual increase in the prevalence of DM from 10% to 12.3% over 17 years.[15–18] Local data have shown that more than half of all amputations in Oman were attributable to DM.[19] In addition, a hospital-based study reported that more than half of Omani patients undergoing coronary artery bypass surgery were diabetics.[20] Moreover, related data indicate an overall high prevalence of traditional CVD risk factors among Omanis.[18,21,22] Therefore, the growing trend of DM and CVD risk factors in Oman have inevitably created challenges for the healthcare system and made CVD a key priority for public health research.

With regards to CVD risk assessment tools, no CVD risk prediction tools have yet been developed for any Arab population, including Omanis. Although, many different CVD risk assessment tools have been developed in other parts of the world (primarily in Europe and the U.S.), these tools are not considered optimal for application among Omani diabetics as well as other Arab populations. This is due to differences in socio-demographic factors, cultures

and lifestyle patterns in these populations, as well as differences in the distribution of various CVD risk factors and CVD incidence. Actually, despite the similarities between the populations from which existing models were derived, developing a model specific for each unique population is a common rationale which gave rise to the existing models. Due to the expected relationship between diabetes and diabetes-related complications with the geographical location of the patient's environment and lifestyle characteristics, existing risk models are not always applicable to different populations; therefore, it is important for each specific population to have its own risk assessment tool.[10,23] Moreover, the lengthy time lag between the development of some of the existing tools and the present, along with major differences in clinical practice, gives rise to questions regarding the validity of applying these risk tools even among populations of similar ethnicities.[10]

In addition, existing tools have not yet been validated in any Arab population, including Omanis. However, as previously mentioned, external validation studies on other diabetic samples have shown that these tools perform poorly when applied to different populations. A study comparing the FG-CVD Risk Profile tool to the WHO/ISH risk prediction charts currently used in primary care institutions in Oman has shown significant discrepancies in risk assessment results between the two tools when applied to a sample of Omani type 2 diabetics, supporting the need for a tool specific for this population.[24] Furthermore, validating various existing tools in this population is time-consuming and not cost-effective, and the results are not expected to differ from those showing poor performance of these tools among different populations. Notably, the WHO/ISH risk prediction charts were not derived from original studies, but using databases related to the prevalence of CVD risk factors and CVD event rates in the Eastern Mediterranean region. This region includes Arab and non-Arab populations and therefore these charts are not specific. Moreover, these charts do not include important traditional CVD risk factors among diabetics such as glycaemic control, DM duration and albuminuria.

In summary, there is a need for a population-specific CVD risk prediction tool for Omani diabetics so as to monitor their CVD risk and inform future treatment and case management strategies.

1.2 Research questions

This thesis project addressed an overall research question and three subsequent questions arising from the main question. The main research question was:

- How can a suitable CVD risk assessment tool be developed to estimate the 5-year CVD risk among Omanis with type 2 diabetes?

The following three questions were developed to answer the main research question:

1- What is the incidence of CVD and the pattern of CVD risk factors among type 2 diabetics in the Aldakhiliyah Governorate (Province) of Oman?

Answering this question was deemed to provide fundamental information on CVD risk in the form of incidence, as well as distribution of CVD risk factors and the key risk factors associated with CVD among this specific population. This would be the base for developing the needed CVD model for this specific population.

2- How can associated CVD risk factors be incorporated into a multivariate model for predicting the 5-year risk of CVD in the type 2 diabetic population in the Aldakhiliyah Province of Oman?

In this regard, the identified independent CVD risk factors among the target population, in addition to their weight of contribution to CVD risk would be incorporated into a CVD risk equation suitable for this specific population.

3- How valid is the developed risk assessment tool to predict the 5-year CVD risk in another cohort of type 2 diabetics taken from the same reference population?

Since it was crucial to test the model, the answer to this question was needed to provide important data related to the validity of the model and its generalisability.

1.3 Aim and objectives

Aim

The ultimate aim of this thesis project was to develop a suitable risk assessment tool to estimate the 5-year CVD risk among Omani type 2 diabetic patients.

Study objectives

The following objectives were developed focusing on the diabetic population of the Aldakhiliyah Province of Oman in order to achieve the overall aim of this research:

- To estimate the incidence of CVD and to describe patterns of CVD risk factors in the type 2 diabetic population in Aldakhiliyah Province of Oman;
- To develop a CVD risk prediction model in the form of a statistical equation suitable to estimate the 5-year CVD risk in the type 2 diabetic population in Aldakhiliyah Province of Oman;
- To validate the accuracy of the CVD risk assessment model developed for type 2 diabetics in the Aldakhiliyah Province of Oman.

1.4 Structure of the thesis

This thesis consists of seven chapters. Chapter 1 summarises the background, rationale, research questions and aim and objectives of the research project, as well as the structure of the thesis. Chapter 2 provides an introduction to the main topic of the thesis and details of a literature review. The last section of Chapter 2 includes a published review article which

summarises the literature and provides critical arguments on the knowledge gap that establishes the context which led to the research questions of the thesis. Chapter 3 presents the detailed research methodologies that were used to answer each research question, including the research design, sampling methods, data collection methods, definitions of the variables, data quality and analysis and ethical considerations. Subsequently, the results of each of the three research questions were presented in Chapters 4, 5 and 6 in the form of published/unpublished papers formatted according to peer-reviewed journal requirements. Each paper includes detailed results as well as a detailed discussion related to the observed findings. Chapter 7 comprises a general discussion on how each research question was answered and how the ultimate aim of the thesis was achieved. In addition, the implications of observed findings, the strengths and limitations of the whole project, in addition to general conclusions and future recommendations, are discussed in this chapter. This thesis format was chosen in accordance with the policy of Griffith University. As a result, there is some repetition of related text in the result chapters as well as the discussion chapter, which is to be expected.

Chapter 2: Literature Review

2.1 Introduction

In the last chapter, the main topic of this project was introduced in addition to a brief rationale that led to the research questions and objectives of this study. In addition, the previous chapter provided a clear idea about the structure of this thesis report.

This chapter forms the second component of this thesis, providing a comprehensive literature review and identifying the gaps in the field and the rationale which led to the context of this project. This chapter provides an overview about type 2 diabetes mellitus (DM), its relationship with cardiovascular disease (CVD) as well as CVD-related complications and CVD risk factors. In addition, it describes the existing global risk assessment tools used to assess CVD risk among type 2 diabetics and their applicability to other populations. The last section of this chapter is comprised of a published review article which addresses the applicability of the current existing CVD risk tools to the Omani type 2 diabetic population.

2.2. Type 2 diabetes mellitus

2.2.1 Definition and etiology

Diabetes mellitus is a multifactorial metabolic disorder characterised by long-term high blood sugar known as chronic hyperglycaemia, resulting from defects in insulin sectretion (type 1), insulin action (type 2) or a combination of these defects, leading to many serious long term complications.[25] Type 1 DM (also known as insulin-dependent DM) affects around 5–10% of the diabetic population. Type 1 DM is an autoimmune disease wherein an immune reaction is elicited against the pancreatic β-cells that manufacture insulin. Gradually, this immune reaction results in the destruction of insulin-producing β-cells.[25,26]

Type 2 DM (also known as non-insulin-dependent DM) represents around 90–95% of the diabetic population. It usually affects adults; however, due to the increasing prevalence of childhood obesity, this type may also occur among children and adolescents.[25,27] The pathophysiology of type 2 DM is initially characterised by high insulin levels due to increased insulin resistance which causes the pancreas to secrete progressively more insulin. Gradually, the insulin starts to decrease to insufficient levels due to pancreatic exhaustion, leading to the accumulation of glucose in the blood which subsequently causes diabetes-related complications.[28–30]

Type 2 DM is a multifactorial disease that arises as a result of the interaction of a number of environmental, genetic and lifestyle factors.[31] Obesity, a sedentary lifestyle and a family history of DM are considered to be common risk factors for the development of type 2 DM.[32,33] In addition, type 2 DM may follow gestational diabetes.[34] Less commonly, type 2 DM may present as an entity in some medical disorders and syndromes, such as acromegaly, hyperthyroidism and Cushing's syndrome.[35–37] Moreover, the risk of type 2 DM may be increased by certain medications, including corticosteroids, thiazides, β-blockers and statins.[38–40]

2.2.2 Global trends and burden of type 2 diabetes

Overall, DM is one of the most common non-communicable diseases worldwide, with a global prevalence of 8.3%; it is considered to be the fourth or fifth leading cause of mortality in most developed countries, whereas in developing countries it is increasingly prevalent and considered an epidemic.[41,42] According to the International Diabetes Federation (IDF), the comparative prevalence of DM in the Middle East and North Africa (MENA), South East Asia and South and Central America regions increased from 9.3%, 7.6% and 6.6% in 2010 to 10.7%, 8.8% and 9.6% in 2015, respectively, while the estimated global prevalence is expected to rise from 8.8% in 2015 to 10.4% in 2040.[42–45] According to the World Health Organization (WHO), more than 422 million people worldwide are currently living with diabetes.[46] Similarly, as illustrated in Figure 2.1, the IDF estimated that the number of people living with DM was 415 million in 2015; this was projected to increase

to 642 million by 2040.[42] Type 2 DM is predominantly a disease of adulthood and the majority of cases occur after 45 years of age.[2] It is thought that the prevalence of diabetes is slightly greater among men under the age of 60–70 years. However, for individuals above this age, it is more common among women.[42,47]

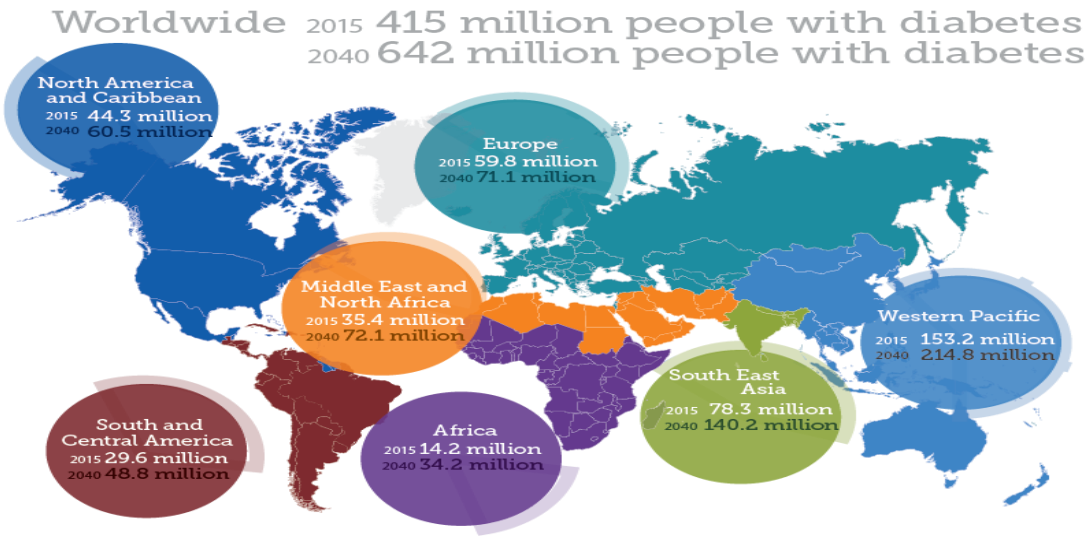

Figure 2.1

Global distribution of type 2 diabetes cases

Source: International Diabetes Federation (online resource, accessed on 29/11/2016).[48]

Notably, the increasing trend of type 2 diabetes worldwide is strongly linked to the increasing rate of obesity.[32,49] Obesity contributes to insulin resistance which is an important component in the pathophysiological mechanism of type 2 diabetes.[50,51] Studies have shown that the risk of pre-diabetes and type 2 diabetes increases with body weight.[52,53] Data have also indicated that there is a particularly high risk of diabetes with abdominal obesity.[54,55] Around 80–90% of all type 2 diabetic cases are thought to be due to both obesity and overweight with abdominally-concentrated fat distribution.[32] Women with a body mass index (BMI) of 23–25 kg/m^2 were found to have a 4-times higher risk of developing type 2 diabetes compared to non-obese women, and women with a BMI of >35 kg/m^2 having a 93-fold increased risk.[54]

Globally, an estimated 1.5 million deaths in 2012 were directly caused by diabetes,[56] and the WHO predicts that DM will be the 7th leading cause of

death worldwide by 2030.[46] Moreover, half of all patients with type 2 DM die prematurely of a cardiovascular cause, while approximately 10% die of renal failure.[2] Moreover, DM imposes a large economic burden on individuals, health systems and governments. Around 10.8% of the total worldwide health expenditure in 2013 was diabetes-related.[42] It is thought that most countries spend between 5–18% of their total health expenditure on diabetes care and related services.[42] Previous research has shown that people with diabetes require at least two to three times as many healthcare resources compared to people without diabetes.[57] In the U.S., the total estimated cost for the care of known diabetic patients in 2002 was estimated at $132 billion compared to $245 billion in 2012, which included $176 billion in direct medical costs and $69 billion in indirect costs.[58,59] In 2008–2009, the Department of Health in Australia allocated around 2.3% of their healthcare expenditure to diabetes care.[60] Therefore, the increasing trend in the prevalence of diabetes and related costs of care will be one of the greatest challenges facing healthcare systems in the near future.

2.2.3 Clinical features and diagnosis of type 2 diabetes

Type 2 diabetics can be asymptomatic for many years before a diagnosis, since insulin resistance and insulin insufficiency occur gradually after the onset of the disease.[28–30] Type 2 diabetes is usually preceded by a state of pre-diabetes when impaired glucose tolerance (IGT) or impaired fasting glucose (IFG)—which are defined as higher than normal blood sugar readings, but not high enough to be diagnosed as type 2 diabetes—are observed. This usually occurs several years before a diagnosis of diabetes is made.[26] Generally, IFG is defined as having a blood sugar reading between 6.1–6.9 mmol/l after fasting for at least eight hours, whereas IGT is defined as having blood glucose levels between 7.8–11.1 mmol/l two hours after eating. People at the pre-diabetic stage have a higher risk of developing type 2 diabetes, especially if obesity is also present.[26,61]

Symptoms related to diabetes may appear only with very high blood sugar levels; these can include polyuria, polydipsia, polyphagia, weight loss, blurred vision and easy fatigability.[25] Susceptibility to various infections may also

occur and an acute life-threatening condition known as ketoacidosis or a non-ketotic hyperosmolar state can also occur with persistent uncontrolled high blood sugar.[26,62,63]

A diagnosis of type 2 DM is usually made from plasma glucose readings despite the presence of other important serum markers like glycosylated haemoglobin (HbA1c).[61] Several organisations have set very similar diagnostic criteria for type 2 diabetes and these include the WHO, American Diabetes Association and European Association for the Study of Diabetes. According to these criteria, a DM diagnosis is made when the fasting plasma glucose concentration is ≥7.0 mmol/l (126 mg/dl) and plasma glucose is ≥11.1 mmol/l (200 mg/dl) two hours following an oral glucose tolerance test or when the HbA1c concentration is ≥6.5%.[25,61,64] Table 2.1 shows the cut-off values for diabetes and pre-diabetes diagnoses.

Table 2.1: Cut-off values used to diagnose diabetes

Condition	Fasting glucose (mmol/l)	OGTT (mmol/l)	HbA1c (%)
Normal	<6.1	<7.8	<6.0
Impaired fasting glucose	6.1–6.9	-	6.0–6.4
Impaired glucose tolerance	-	7.8–11.1	6.0–6.4
Diabetes mellitus	**≥7.0**	**≥11.1**	**≥6.5**

Abbreviations: OGTT, oral glucose tolerance test; HbA1c, glycosylated haemoglobin.

2.2.4 Management of type 2 diabetes

Patients with type 2 diabetes should receive integrated management from a team of healthcare professionals that may include physicians, nursing practitioners, podiatrists, dieticians, health educators, pharmacists and mental health professionals with expertise and a special interest in diabetes.[26,63] Also, diabetic patients should play an active role in their own care since most management plans require individualised goals and treatment plans which take the patient's preferences into account. In this context, the patient's age, working conditions, physical activity level, diet, social status and cultural

characteristics should all be considered, as well as the presence of diabetes-related complications or other medical conditions. In addition, education on diabetes self-management and ongoing diabetes support should be included as an integral component of patient care,[26,63]

Three main aspects should be targeted in the treatment of diabetes: glycaemic control, the evaluation of micro-vascular and macro-vascular complications and the minimisation of cardiovascular and other long-term risk factors.[26,63,65] Glycaemic control needs effective assessment, monitoring and intervention; this can be achieved by a combination of patient self-monitoring of blood glucose, HbA1c measurements and continuous interstitial glucose monitoring.[26] Glycaemic management should be directed to keep HbA1c concentrations below or around 7.0%, fasting blood glucose at 3.9–7.2 mmol/l and peak post-prandial blood glucose under 10.0 mmol/l. However, these goals should be individualised based on DM duration, the presence of comorbidities, age/life expectancy based on population data and other related factors.[26]

Glycaemic control may be achieved through one or a combination of modalities including non-pharmacological and pharmacological approaches. In fact, management of type 2 diabetes is not limited to pharmacological interventions alone, but can include non-pharmacological aspects such as regular moderate-intensity physical activity and healthy dietary patterns; these factors can contribute significantly to glycaemic control, especially in overweight and obese patients.[66,67] Regular exercise has been found to improve glycaemic control in all forms of diabetes by reducing insulin resistance and the hepatic production of glucose.[68] A Mediterranean-style diet has been found to be an effective way to lower body weight, HbA1c, low-density lipoprotein cholesterol (LDL-C) levels, oxidative stress and improve high-density lipoprotein cholesterol (HDL-C) levels; all of which are beneficial to the prognosis in type 2 diabetes cases.[69] In addition, moderate physical activity and adequate dietary protein intake (≥0.8 g/kg/day) should be included in recommendations for prevention of DM complications and better metabolic control among older adults with type 2 diabetes.[68,70] Moreover, bariatric

surgery may be considered as a treatment option for very obese diabetic patients to control diabetes and common co-existing hypertension (HTN).[68]

With regards to pharmacological modalities in the management of diabetes, clinical guidelines recommend metformin as the first line of treatment for patients with type 2 diabetes, especially if they are overweight or obese.[26,71] Alternatively, sulfonylureas (e.g. gliclazide and glibenclamide) can be used as other first-line treatments in some selected conditions like intolerance or contraindication to metformin; however, these are generally used as the second line of therapy when targeted glycaemic control cannot be achieved by metformin.[26,71] Dipeptidyl peptidase-4 (e.g. sitagliptin and vildagliptin) can be used as second-line therapies with sulfonylureas or as a third-line treatment in combination with metformin if the targeted glycaemic level cannot be achieved.

Thiazolidinediones (e.g. pioglitazone) can be used as a second-line therapy with metformin instead of sulfonylureas if the risk of hypoglycaemia is high or if the patient is considered at high risk, for example when living alone. They can also be used as a third line of therapy with metformin and sulfonylureas to achieve optimal glycaemic control. Glucagon-like peptide mimetics-1 (e.g. exenatide) can be used as a third-line therapy addition to metformin and sulfonylureas, especially for obese patients or if insulin therapy has major implications for patients with long working hours whom might prefer a single-dose medication. On the other hand, insulin therapy is the ultimate treatment for patients with type 2 diabetes when the aforementioned interventions are not effective. There are several different insulin regimes depending on the target set for each patient. However, a twice daily dose of intermediate-acting insulin or a single daily dose of long-acting insulin analogue are good starting options that need to be titrated until glycaemic control is achieved.[26,71] Additionally, the need for short-acting insulin can be determined according to blood sugar profile and the patient's other circumstances.[26,71]

2.2.5 Type 2 diabetes in the Middle East, Arabian Gulf Countries and in Oman: Major challenges

In the Middle Eastern region, the prevalence of diabetes is reportedly 10.7%, which is considered to be the second highest prevalence of all regions worldwide.[42] According to the estimates of the IDF, about 35.4 million people with diabetes currently live in this region and this number is expected to double by 2040. Furthermore three of the top ten countries in the world with the highest prevalence of diabetes in 2013 were located in the Arabian Gulf (Saudi Arabia, Kuwait and Qatar).[72]

The Arabian Gulf is a part of the Arab world located in the Middle East and North Africa (MENA). Rapid economic development and major social changes coupled with ageing populations have occurred in the Arabian Gulf countries over the last four decades. These challenges have resulted in a dramatic increase in the prevalence of type 2 DM and other non-communicable diseases in the region.[72] Rapid urbanization, reduced infant mortality and an increasing life expectancy along with negative behavioral and lifestyle changes such as unhealthy diet and physical inactivity have contributed to the increased rates of obesity and related health consequences.[72,73]

Many studies were conducted on the prevalence of diabetes in the Middle East, where it largely differed across studies depending on the study populations and the definitions of diabetes in different studies In this regard, a systematic review showed an increasing trend in diabetes prevalence for most countries in the MENA region. The highest increase was observed among Arabian Gulf countries. In Saudi Arabia, the prevalence of diabetes increased from 9.4% to 22% in males and from 8.7% to 21.7% in females between 1980 and 2008.[74] Some recent studies have shown varying DM prevalence rates in different target populations in the Arabian Gulf as well as other Arabian countries as follows: 31.6% among urban residents of Riyadh in Saudi Arabia,[75] 21.4% among employees surveyed in Kuwait,[76] 16.7% among healthcare center users in Qatar,[77] 18% in a population screening program in the United Arab Emirates,[78] 17.1% among urban dwellers in Jordan,[79] and 15.8% among a representative study sample in Beirut, Lebanon. [80]

It seems that the prevalence of diabetes will continue to increase in this region for two main reasons. First, pre-diabetes notably affects a large proportion of people in this region (7.8%), including 16.8% in Iran and 27% in the United Arab Emirates.[42,78,81] Second, certain data have suggested that the prevalence of type 2 diabetes is high among children in this region.[82]

Oman is an Arab Gulf country located in the south-eastern corner of the Arabian Peninsula, with a land area of 309,500 km^2 and a total population of 3.855 million, of which 2.172 million are Omani citizens.[83,84] The Omani population is relatively young—nearly 44.6% of Omani citizens are younger than 20 years of age and only 5.9% are older than 60 years—with an annual population growth rate of 3.7% according to national statistics.[84]

Over the past four decades, the overall main focus of public health in Oman has evolved gradually from infectious diseases to non-communicable chronic diseases which now pose the main challenge to the country.[85] Currently, more than 75% of the disease burden in Oman is attributable to non-communicable diseases. This change in population health trends in the country is due to the marked reduction in the incidence of infectious diseases, rapid economic development and improvements in healthcare and socioeconomic factors, which have resulted in a sharp decline in infant and early childhood mortality and a dramatic increase in life expectancy.[85]

The increasing trend of diabetes in Oman has been evidenced in many studies. Three consecutive epidemiological surveys conducted in Oman have shown a gradual increase in the prevalence of DM from 10% in 1991 to 11.6% in 2000 and 12.3% in 2008.[15–18] In addition, the age-adjusted prevalence of diabetes among Omanis aged 30–64 years old increased from 12.2% in 1991 to 16.1% in 2000.[17] Furthermore, the diabetes prevalence in Oman increased considerably according to age group from less than 1% among 18–24-year-olds to 35% among 55–64-year-olds.[18] Moreover, local data have shown that the prevalence of DM among urban residents is much higher compared to rural populations (17.7% vs. 10.5%).[86] Figure 2.2 illustrates the gradual increase in the national prevalence of diabetes in Oman up until 2015 in comparison with other Arabian Gulf countries.[17,18,42] The increasing

prevalence rates from 1991 to 2008 was based on local data; however, the lower prevalence in 2015 was sourced from IDF estimates.

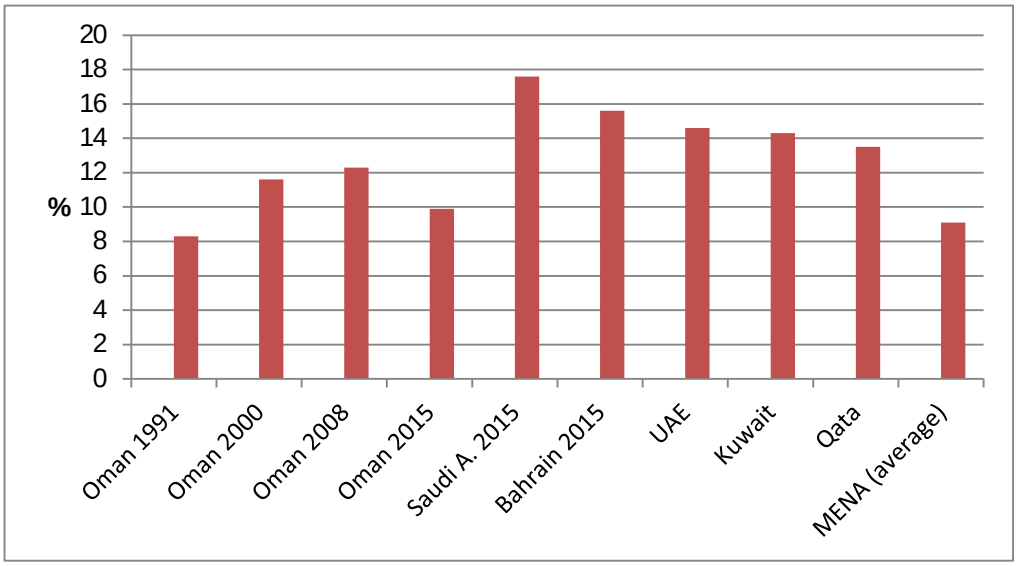

Figure 2.2

The prevalence of type 2 diabetes in Oman and selected Arabian Gulf countries

Source: Adapted from local and International Diabetes Federation data.[17,18,42]

Abbreviations: Saudi A., Saudi Arabia; UAE, United Arab Emirates; MENA, Middle East and North Africa.

In addition, the number of people living with diabetes in Oman is expected to increase by 190% from 75,000 in 2000 to 217,000 in 2025, as estimated by the WHO.[87] According to the Oman Ministry of Health's annual report in 2015, a total of 87,064 diabetic patients were registered in the National Diabetes Registry.[88] Figure 2.3 illustrates the number of new cases registered annually at the national level in the last eight years.[89] As type 2 diabetes is a long-lasting chronic disease, it is expected that the prevalence will inevitably increase if the incidence of the disease continues according to the current trend of registered cases.

On the other hand, risk factors for type 2 diabetes are another major concern in Oman. The high rate of pre-diabetes together with high overweight and obesity rates in the Omani population make it likely that diabetes will continue to pose a major health problem and a significant challenge to the national

healthcare system in the near future. In this regard, the results of two surveys showed the prevalence of IFG and IGT pre-diabetes among Omani adults to be as high as 35% and 17.3%, respectively.[90,91] In addition, a community-based survey showed the prevalence of IFG alone to be around 4.4%.[18] As for obesity (a common risk factor for DM), a survey showed that nearly half of the study population were overweight or obese,[17] whereas more recent data showed that 30% of Omani adults were overweight and about one-quarter were obese.[18] Therefore, the growing trend of overweight/obesity inevitably complicates the issue of non-communicable disease and type 2 diabetes and is likely to further impact the Omani healthcare system and economy in the near future.

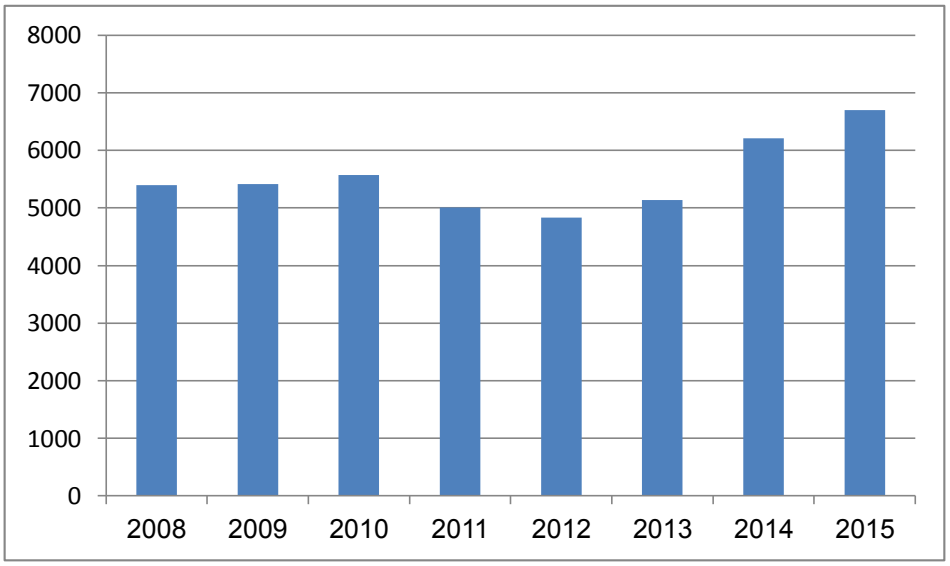

Figure 2.3

Annual number of new type 2 diabetes cases registered in Oman from 2008–2015

Source: Annual health reports (2008–2015), Ministry of Health, Oman.[89]

2.3 Complications of type 2 diabetes

2.3.1 Overview

The direct and indirect effects of diabetes on the human vascular tree are a major source of morbidity and mortality in both type 1 and type 2 DM. In

general, diabetes-related complications are categorised into two main types: micro-vascular and macro-vascular complications. Diabetic micro-vascular complications include diabetic nephropathy, neuropathy and retinopathy, while macro-vascular complications include coronary heart disease (CHD), peripheral arterial disease (PAD), and stroke.[41,63,92,93] In addition, other less common cardiac complications of type 2 diabetes include diabetic cardiomyopathy and heart failure.[41,63,92]

2.3.2 Macro-vascular complications of type 2 diabetes

2.3.2.1 Overview and pathophysiology

A large number of studies have demonstrated that CHD, stroke and PAD are the main macro-vascular complications associated with type 2 diabetes and constitute the majority of CVD conditions in type 2 diabetic populations.[2,94–97] The process of atherosclerosis is thought to result from chronic inflammation and injury to the arterial walls leading to the narrowing of these walls throughout the body.[92] This process is the central pathological mechanism in all three CVD entities.[92] In addition to the formation of atheroma, platelet adhesion, impaired fibrinolysis and hypercoagulability are among the other processes that further increase the risk of vascular occlusion and cardiovascular events in type 2 diabetics, as illustrated by several studies.[97,98] Furthermore, type 2 diabetes typically occurs in the setting of metabolic syndrome, a group of conditions which includes abdominal obesity, HTN, hyperlipidaemia and increased coagulability; these are thought to encourage the pathophysiology of CVD in this risky population.[99]

Globally, more than 17 million deaths annually are attributed to CVD in the general population, of which around 7 million are due to CHD and more than 5 million are due to cerebrovascular disease.[100] Cumulative incidence data from New Zealand have indicated that 17.9% of type 2 diabetics experienced their first CVD event within a median period of 4 years, while in Australia 14.9% of diabetics developed their first CVD event within a mean follow-up period of around 5 years.[101,102] However, incidence data from China have indicated a much lower rate (4.9%) within a similar median follow-up period.[103] Among the

type 2 diabetic population, it is estimated that half of all patients die prematurely of a cardiovascular cause.[2] In both type 1 and type 2 DM populations, CVD is considered the primary cause of death.[104,105]

As regards the burden of disease on healthcare systems, CVD among people with diabetes accounts for the greatest component of healthcare expenditure.[58,105] According to the updated 2014 statistical report of the American Heart Association, the burden of CVD in the general population remains high despite a decline in attributed mortality.[106] In this context, the mortality attributed to CVD was observed to decline by 31% from 2000 to 2010; however, CVD still accounted for around 32% of all deaths in 2010.[106] In a study comparing type 2 diabetic patients with a group of controls matched by year of birth and gender, the annual cost of care for diabetic patients with cardiovascular complications was approximately 2.3 times higher than that for diabetic patients without CVD and approximately four times higher than the cost for people with neither type 2 diabetes nor CVD.[107]

2.3.2.2 Coronary heart disease among type 2 diabetic populations

CHD occurs as a result of the atherosclerotic stenosis of one or more arteries supplying blood to the myocardium. This can cause partial ischemia or complete arterial occlusion, leading to a myocardial infarction.[97,108–110] Clinical features of CHD may include epigastric pain, chest discomfort and dyspnoea. A clinical diagnosis is usually made using electrocardiography (ECG) and measurement of the levels of serum cardiac enzymes, including troponin. In some instances, more sophisticated techniques are required to confirm the diagnosis, such as an ECG stress test, coronary angiography and other imaging studies like coronary computed tomography (CT) and magnetic resonance imaging (MRI).[109,110]

CHD is common among diabetics, especially among older patients. In a large population-based survey conducted in the U.S., the prevalence of CHD among those aged 50 years and older rose from 8.7% among non-diabetics to as high as 19.2% among diabetics with metabolic syndrome.[111] Another population-based study showed that the seven-year incidence of the first

myocardial infarction or death was around 20% among diabetics compared to 3.5% among non-diabetics.[95] Diabetics are thought to have a two-to-four-fold increase in the risk of CHD compared to people without diabetes.[97] The results of a recent study showed that, after adjusting for age, the risk of hospitalisation due to a heart attack was 1.8 times higher among diabetic adults of 20 years of age and above than that of non-diabetic patients in the U.S.[59] Moreover, patients with diabetes also have an adverse long-term prognosis after a myocardial infarction, including increased rates of re-infarction, congestive heart failure and death.[112]

2.3.2.3 Stroke among type 2 diabetic populations

A stroke is a neurological injury resulting from disturbed blood supply to the central nervous system. It is defined as a rapid-onset focal neurological deficit lasting longer than 24 hours, with no apparent cause other than disruption of blood supply to the brain. It is classified into two major types: brain ischaemia due to thrombosis, embolism or systemic hypoperfusion, and brain haemorrhage due to intracerebral or subarachnoid haemorrhage.[113,114] Clinical features of stroke may include headaches, vomiting and a decreased level of consciousness along with focal neurological deficits depending on the site of the affected brain tissue.[114] A diagnosis of stroke is usually made by a combination of proper history-taking, physical examination and imaging studies like CT and MRI.[114]

General population-based statistics have shown that the overall prevalence of stroke in the U.S. is 2.8%.[106] Globally, the incidence of ischaemic stroke is much higher than that of the haemorrhagic type in the general population. Ischaemic strokes constituted 68% of people who have experienced strokes while haemorrhagic strokes constituted 32%.[113] However, a higher incidence of haemorrhagic stroke has been reported in low- and middle-income countries.[115] Among type 2 diabetic populations, the prevalence of stroke is around 4–12% in clinic-based studies and around 4–5% in population-based studies.[116] Other data suggest that diabetes is present in about 10–25% of people with a history of stroke.[117] In addition, diabetic patients were found to have a five-fold higher prevalence of calcified carotid atheroma compared to

an age-matched non-diabetic control group.[118] Moreover, data from a cohort study showed that the risk of stroke was increased almost three-fold among diabetics compared to non-diabetics.[92,119] It is estimated that around 80% of people with diabetes will die from a heart attack or stroke, of which 20% of deaths are due to stroke, making it one of the leading causes of death in this population.[120,121]

2.3.2.4 Peripheral arterial disease among type 2 diabetic populations

PAD refers to the obstruction of large arteries other than the coronary arteries, the aortic arch vasculature and the cerebral arteries.[122,123] Patients with PAD often have no clinical complaints during the initial stages of the disease. However, patients may become symptomatic when the blood supply fails to fulfil ongoing metabolic requirements as a consequence of arterial narrowing. PAD can present with intermittent claudication, a condition which causes pain in one or more of the lower extremity muscles when undertaking physical activity. However, patients may also present with pain at rest, non-healing wounds, ulceration or gangrene in more advanced cases.[124,125] A diagnosis of PAD is usually made by combining several clinical findings with diagnostic modalities like the ankle-brachial pressure index (ABPI). The ABPI is a simple, accurate and relatively inexpensive test used to screen for PAD; it assesses the ratio of systolic pressure in the lower versus upper extremities using a Doppler ultrasound.[126,127] However, other investigations such as segmental pressure and pulse volume recordings, exercise treadmill tests and vascular imaging modalities may be needed for further assessment and to aid treatment of the condition.[128]

As in CHD and stroke, the risk of PAD in diabetics is thought to be more than 2.5 times higher than for non-diabetics.[129] Related data have indicated that an estimated 8.1% of the diabetic population aged 40 years and older have PAD in comparison to 4.0% among those without diabetes.[130] In addition, a significant proportion of patients hospitalised with PAD are diabetic.[63] Moreover, in developed countries, lower limb amputations are at least 10 times more common in people with diabetes than in non-diabetic individuals.[57]

2.3.3 CVD among people with type 2 diabetes in Oman

Information related to the trend and burden of CVD in Oman is very limited for both the diabetic and general population. In the World Health Survey conducted in 2008 on the general population, the prevalence of cerebral stroke among Omanis was found to be 0.6% and angina pectoris was 1.5%.[18] Data collected from the general population showed that CVD was ranked as the first leading cause of death, accounting for 43% of total mortality and the third highest cause (13%) of disability-adjusted life years lost.[85] In 2011, CVD accounted for a lesser proportion (33%) of total mortality than in 2002. However, it is still considered to be the leading cause of death in the country.[20,131] In addition, CVD accounted for 29.8% of the total causes of death in 2013, according to the Ministry of Health.[83]

There is very limited literature related to CVD with regards to the type 2 diabetic population in Oman. CHD was identified in 1.6% and 1.4% of newly diagnosed diabetic patients in 2013 and 2015, respectively.[83,88] Data in 2005 showed that more than 50% of amputations in Oman were attributed to DM.[19] The high prevalence of DM among acute CHD patients indicates an alarming trend for poor disease prognosis.[85] In this regard, 54.1% of Omani patients receiving a coronary artery bypass surgery were diabetic,[20] while in an analysis of the Gulf Registry of Acute Coronary Events study, data from Oman showed that 36% of patients with acute CHD were diabetic.[132]

2.4 Risk factors and predictors of CVD among type 2 diabetics

It is evident that the early diagnosis of diabetes and other risk factors for CVD is key to delaying or preventing the onset of CVD through targeted interventions.[26,133–136] The delayed recognition of various forms of CVD undoubtedly worsens the prognosis for survival for many diabetic patients. Although there are many common CVD risk factors shared both by diabetics and the general population, patients with diabetes are more susceptible to atherogenic risk factors than non-diabetics, and the CVD risk due to these factors is thought to be aggravated among this patient group.[137–139] Among type 2 diabetics, many traditional CVD risk factors such as HTN, dyslipidaemia, smoking, poor glycaemic control, albuminuria, DM duration,

male gender and physical inactivity have been identified as independent risk factors for the development of CVD. However, other newer predictors (also known as non-traditional factors)—such as unhealthy dietary patterns and erectile dysfunction, as well as other inflammatory, haematological and thrombogenic markers—were identified in more recent studies to be associated with CVD among diabetics.

The risk of CVD among diabetics varies widely with the intensity of various risk factors. In some studies, up to 75–90% of CVD events were found to be attributable to traditional risk factors.[4,5] In this context, HTN and dyslipidaemia are thought to be more important than other traditional factors, including glycaemic control.[140] On the other hand, non-traditional factors were found to have a relatively small contribution to CVD risk. Currently, there is insufficient evidence to suggest that routine monitoring of the non-traditional predictors leads to better diagnostic and therapeutic results in diabetic patients.[3,141,142]

2.4.1 Traditional CVD Risk Factors among type 2 diabetics

Although there is some degree of consistency in the categorisation of CVD risk factors among review studies of the general population, review studies of type 2 diabetics are limited in this regard.[3,143] In addition, these reviews do not include all recent original studies related to the identification of CVD risk factors among type 2 diabetics. Therefore, in addition to review articles, recent studies were also evaluated; these revealed that HTN, dyslipidaemia, glycaemic control, male gender, age, physical inactivity, smoking, early renal disease markers, DM duration, ethnicity and a family history of CVD are the most commonly identified traditional predictors for CVD among diabetics.[3,101–103,141,143–146] Although obesity has not been commonly identified as an independent risk factor among diabetics in these studies, it is a well-known traditional risk factor in the general population and therefore it can be included in this group as well.[147–149]

Hypertension is a very strong predictor for CVD among diabetics and non-diabetics, and related data have shown that HTN quadruples the CVD risk in diabetic patients.[95,150] Blood pressure (BP) control in patients with type 2

diabetes has been associated with a significant decrease in CVD events and mortality.[134,151] In fact, the U.K. Prospective Diabetes Study (UKPDS) demonstrated a reduction in macrovascular disease of 24% among type 2 diabetics with strict HTN control (BP of 144/82 mmHg) compared to those with less strict control (BP of 154/87 mmHg).[134] Strict management of HTN among both diabetics and non-diabetics has been recommended and incorporated as a fundamental part of CVD prevention and management in various professional guidelines, including those distributed by the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure, the American Diabetes Association and the European Society of Hypertension/European Society of Cardiology.[1]

Dyslipidaemia, which can present as high LDL-C levels, high triglyceride (TG) levels, low HDL-C levels, or a high level of total cholesterol, is significantly associated with CVD in both diabetics and non-diabetics.[136,152] In fact, the role of statin therapy for the management of diabetic dyslipidaemia in reducing CVD events has been analysed in a large number of clinical trials, like the Collaborative Atorvastatin Diabetes Study, the Heart Protection Study and the Action to Control Cardiovascular Risk Factors in Diabetes trial.[153–155] Observational studies have shown that HDL-C levels may be the most consistent predictor of CHD in type 2 diabetics, followed by TG levels and total cholesterol.[136] Similarly to HTN, the management of dyslipidaemia in reducing CVD events among diabetics has been incorporated in various professional guidelines such as those from the American Diabetes Association.[136]

Obesity-related studies in the general population have shown a positive independent relation between obesity and CVD.[147–149] The Framingham Offspring Study has shown that BMI significantly and independently predicted the occurrence of CHD and stroke after adjusting for traditional risk factors.[147] However, studies among diabetics have revealed different results. While some studies have reported that obesity has an insignificant role in CVD occurrence,[156,157] other studies have shown a significant positive relation with

BMI.[142,145] Therefore, there is still some controversy regarding the independent role of obesity in CVD occurrence among diabetics.[3,158] On the other hand, obesity is also part of metabolic syndrome, which is defined as having three or more of the following five cardiovascular risk factors: central obesity (defined as increased waist circumference), elevated TG levels, low HDL-C levels, HTN and elevated fasting glucose.[159] In type 2 diabetic patients, central obesity with any one of the remaining factors is enough to fulfil the criteria of metabolic syndrome. This has been found to be associated with a major increase in CVD risk beyond the sum of the effects of the individual factors.[160] However, as far as metabolic syndrome is concerned, two large meta-analyses have shown that metabolic syndrome raises the risk of CVD by approximately two-fold.[161,162]

Poor glycaemic control in diabetic patients is also considered to be a major risk factor for all diabetes-related complications, and its treatment plays an important role in reducing CVD risk.[163] Elevated HbA1c appears to correlate significantly with mortality and cardiovascular events in a linear manner, whereby a 1% increase in HbA1c has been found to increase the risk of cardiovascular events or deaths by 20–30%.[164] This risk exists for CHD, fatal and nonfatal myocardial infarctions, stroke and, perhaps most strongly, PAD among patients with both type 1 and type 2 diabetes.[163] Elevated HbA1c is consistently associated with an increased risk for adverse cardiovascular outcomes, although the magnitude of increased risk varies substantially between different study settings. For example, a 1% increase in HbA1c was associated with an increase in stroke risk ranging from 0–30%.[143] In addition, in an epidemiologic assessment of the relationships between glycaemic control and all-cause mortality, it was found that a 1% increase in average HbA1c was associated with a 22% higher risk of death.[165]

Physical activity encompasses recreational/leisure-related activities, transportation (e.g. walking or cycling), occupational activities (i.e. work), household chores, play, games, sports or planned exercise in the context of daily, family and community activities.[166] There is considerable evidence that

physical activity plays an important role in the occurrence of CVD in both the general and diabetic population.[167–170] One study found that diabetics who walked at least two hours per week had a 39% lower all-cause mortality rate compared with inactive individuals with diabetes.[169] However, it should be noted that the effect of physical activity can be confounded by other lifestyle changes that take place together with exercise (for example, smoking cessation, eating a balanced diet, etc.).[3] In addition, physical inactivity can have an indirect effect on CVD risk by affecting other risk factors like HTN, dyslipidaemia, obesity and glycaemic control.[171]

Smoking is linked with a deterioration in metabolic control among diabetic patients, which is subsequently associated with an increased risk of CVD and mortality.[172–174] In a prospective cohort of female type 2 diabetic nurses, cigarette smoking was found to be strongly associated with the risk of CHD; additionally, this risk was reduced with a corresponding decrease in the number of cigarettes smoked per day. Compared with those nurses who had never smoked, the relative risk for CHD was found to be 2.68 (95% confidence interval [CI]: 2.07–3.48) for current smokers who smoked 15 cigarettes per day or more.[175] Another large prospective study examining the effects of smoking cessation on CVD risk in diabetic patients revealed that smoking cessation decreased mortality risk among diabetics; however, it was observed that the risk kept increasing for some years after stopping and was highly dependent on smoking duration.[176]

Male gender has been found to be linked to CVD in both the general and the diabetic population. In the general population, epidemiological data from the Framingham Heart Study (FHS) showed a later onset and lower prevalence of CVD among women.[177] Data from a clinical trial indicated that females had a 20% lower risk of CVD compared to males after adjusting for treatment and other factors.[178] Among diabetics, various studies have shown similar results.[102,103,141,145,146] The findings of the UKPDS have shown that females have half the risk of developing CVD compared to males, while the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled

Evaluation (ADVANCE) study estimated the CVD risk among females to be 0.62 of the male risk.[141,146]

Age, both in general and at diagnosis of type 2 DM, has been demonstrated to be an independent risk factor for CVD in both the general and diabetic populations in many studies.[102,141,142,144–146,179–182] Among type 2 diabetics, an Australian longitudinal study on CVD risk assessment found a significant difference between the mean current age of diabetics who developed CVD compared to those who did not (62.8 vs. 71.4 years; *P* <0.001). A similar Chinese study illustrated a significant increase in CVD risk (2.67%) for each one year increase in age.[103] Similarly, age at DM diagnosis has been found to be linked to CVD in most related studies conducted among diabetics. The ADVANCE study showed that the risk of CVD increased significantly by 6.2% for each one year increase in age at DM diagnosis (*P* <0.001). In the Swedish National Diabetes Register (SNDR) study, the hazard ratio of CVD was found to be 1.066 (95% CI: 1.057–1.075) for a one year increase in the age at diagnosis among type 2 diabetics.[145]

Biomarkers for early renal disease, in the form of proteinuria (macro- or micro-albuminuria) or decreased glomerular filtration rate (GFR), have consistently been shown to be strong predictive markers for cardiovascular events and mortality.[3,183–185] However, as emphasised in several recent reviews, proteinuria as a measure of renal dysfunction is generally a stronger predictor of adverse cardiovascular outcomes than reduced GFR.[3,143] Patients with micro-albuminuria are at very high vascular risk and should be placed under strict risk factor control.[186] As demonstrated by a related study, CVD risk has been found to increase with increasing levels of proteinuria, with a CVD hazard ratio of 1.24 (95% CI: 1.18–1.32) for micro-albuminuria and 2.01 (95% CI: 1.86–2.17) for macro-albuminuria.[101]

Diabetes duration has been found to be strongly associated with CVD in many related studies, independently of age and other risk factors.[101,103,141,144,145] In the Chinese Total CHD Risk Score and ADVANCE

studies, CVD risk was found to increase by 4% and 8%, respectively, for each one year increase in diabetes duration.[103,141]

Ethnicity plays an important role in CVD risk among diabetics in multi-ethnic populations, as demonstrated in many studies.[101,102,142,146] In the Australian Fremantle Diabetes Study (FDS), being an indigenous Australian was found to be a risk factor for CVD, while being of Southern European descent was found to be a protective factor.[102] In the UKPDS, Afro-Caribbean diabetics were 0.39 times less likely to develop CVD compared to Caucasians and Asian-Indian diabetic patients.[146]

A family history of CVD is a well-established risk factor for CVD in the general population.[159,182,187,188] However, while some studies have emphasised a family history of early-onset CHD (age at onset of <55 years for men and <65 years for women) in a first-degree relative, other studies have established the role of a family history of CVD regardless of age at onset in the development of CVD events.[187] Among diabetics, a study has shown that the co-existence of diabetes and a family history of early-onset CHD has a very strong impact on CVD risk, to the extent that diabetics with a family history of CVD were 21.3 times (95% CI: 9.1–50.0) more likely to develop CHD compared to non-diabetics with no family history of CVD. However, diabetics without a family history had a relative risk of 2.8 (95% CI: 1.6–4.9) compared to the same reference group.[189]

2.4.2 Non-traditional predictors for CVD among type 2 diabetics

In addition to classical factors, other less commonly identified predictors—a combination of risk factors and biomarkers—have been found to be linked with increased CVD risk among type 2 diabetics.[190] Due to the limited role of these factors in the development of CVD and their limited utility in CVD risk assessment, they are discussed briefly in the following section.

Specific dietary patterns like the consumption of nuts and whole grains have been found to be related to CVD risk. Data from the Nurses' Health Study have demonstrated that consumption of >5 portions of nuts/peanut butter per

week led to a significantly reduced risk of CVD and myocardial infarction.[191,192]

Erectile dysfunction among men has been found to be associated with an elevated risk of CVD events in some studies.[193,194] In a case-control study, the prevalence of erectile dysfunction was significantly higher among diabetic patients with silent CHD than in those without silent CHD (33.8% versus 4.7%; *P* <0.001).[194]

In addition, **retinopathy** has also been found to be associated with CVD among diabetics. In a population-based cohort study, the presence of diabetic retinopathy was associated with a two-fold higher risk of incident CHD events and a three-fold higher risk of fatal CHD.[195] In the ADVANCE study, retinopathy was also found to be a significant risk factor for CVD with a hazard ratio of 1.47 (95% CI: 1.20–1.79) compared to patients without retinopathy.[141]

Moreover, a number of **metabolic, thrombotic, hematological and inflammatory biomarkers** have been studied and shown a positive relationship with CVD among diabetics. As summarised by recent reviews, these biomarkers include insulin resistance/hyperinsulinemia, homocysteinemia, total white blood cell count, factor VIII, plasma fibrinogen and C-reactive protein.[3,196]

2.4.3 Studies on CVD risk factors among type 2 diabetics in Oman

Studies related to CVD risk factors in Oman are almost all descriptive in nature with regards to the trend of well-known factors; moreover, most of the results are related to the general population. One matched case-control study was previously conducted to assess significantly associated risk factors of CHD in the general male Omani population.[197] Ganguly *et al*. conducted a hospital-based matched case-control study among male Omani CHD patients admitted to two large tertiary hospitals to assess associated risk factors with CHD outcome.[197] It was found that the majority of cases (96%) were above 40 years of age. Sedentary lifestyle was very common (88.0%) among the

studied sample. HTN, DM, a family history of CHD and a sedentary lifestyle were the most significant risk factors for the development of the disease.

While many studies have been conducted to describe trends of well-known traditional CVD risk factors among the Omani general population, few have included the diabetic population. The National Health Survey conducted in 2008 among Omani adults showed that around one-third were overweight, one-quarter were obese, 40% were hypertensive, 33.6% had hypercholesterolemia, 35.2% had low HDL-C levels, 32% had high LDL-C levels and 18% had high TG levels.[18] In another study, the age-adjusted prevalence of metabolic syndrome in the general adult Omani population was 21.0%. Low HDL-C levels were the most common component (75.4%) in the study sample, followed by abdominal obesity (24.6%) which was markedly higher in women than in men (44.3% vs. 4.7%).[198] Other data have also reported the prevalence of current smoking in the Omani adult population to be 7.0% (13.4% among males and 0.5% among females).[199] As for physical inactivity, available data indicate that it occurs in 33% of Omani men and 41% of Omani women, with the proportion of leisure time inactivity reaching 55.4%.[21,22]

Studies describing the picture of risk factors in Omani patients with CVD are very limited in the existing literature. A study conducted among 146 patients receiving coronary artery bypass grafting surgeries at the Sultan Qaboos University Hospital in Oman showed that HTN dyslipidaemia, male gender, diabetes, old age (above 60 years old), a history of smoking, obesity and a history of CHD were present in 81.51%, 78.77%, 73.29%, 54.11%,47.95%, 28.08%, 21.23% and 13.01% of the study sample, respectively.[20]

A literature search revealed that no analytic studies have yet been conducted to assess CVD risk factors in the Omani diabetic population. However, there are some data available regarding the distribution of well-known traditional risk factors among this specific group in Oman. The National Annual Health Report indicated that 27.4% of newly diagnosed diabetic patients in 2015 were hypertensive at the time of diagnosis.[88] Data from a cross-sectional study showed that over 80% of type 2 diabetics were overweight or obese

(BMI of ≥25 kg/m^2), 52% were on anti-hypertensive drugs, 40% were on lipid-lowering drugs and 70% had poor glycaemic control.[200] A study of a random sample of Omani type 2 diabetics assessing risk factors for diabetic nephropathy revealed that 52.2% were hypertensive, 56.7% had uncontrolled glycaemia, 44.1% had hypercholesterolemia, 71.8% had high LDL-C levels, 20.8% had low HDL-C levels, 21% had high TG levels, 38.6% were overweight and a similar proportion were obese. Overall, 65.5% of the sample were aged 40 years or over at their DM diagnosis, 26% were older (>60 years) and around 20% had had diabetes for 10 years or longer.[201] The 2008 National Health Survey indicated that the prevalence of uncontrolled diabetes (HbA1c of >7%) was 64% among the diabetic subpopulation of the survey.[18] Another descriptive study conducted on type 2 diabetics in primary care institutions revealed similar results regarding uncontrolled diabetes.[202] Moreover, data on the prevalence of diabetic nephropathy showed that 42.5% of Omani diabetics had micro- or macroalbuminuria.[203] However, another study revealed the prevalence of micro-albuminuria alone to be 27% among type 2 diabetics attending the outpatient clinic of a tertiary care institution.[204]

In summary, despite the limited available literature, existing evidence indicates a high prevalence of CVD risk factors among both the general and diabetic populations of Oman. This poses considerable challenges for the national economy and healthcare system with regards to the long-term impact of CVD in these populations.

2.5 Global CVD risk assessment tools for type 2 diabetics

2.5.1 Overview

In general, risk assessment tools are mathematical models or charts used to estimate the risk of a condition/outcome event in an individual. They are usually based on the predictive information available for the various risk factors of the specified condition. In these mathematical models, the standardised coefficient of each included risk factor indicates its relative contribution to the overall risk. Usually, such models are used for two main purposes: diagnostic, wherein they are used to estimate the current risk of a

disease or health event, and prognostic, wherein they are used to predict the future risk of a particular disease or health event within a given time period.[205]

In the context of CVD, such models are usually used to estimate the 5-year or 10-year risk of CVD, which can then be used to assess the prognosis and support the choice of preventative and therapeutic strategies for at-risk individuals, either in general or diabetic populations. Choosing between the 5-year or the 10-year risk is not a major concern since both are practical, however, the 5-year risk is thought to be more accurate compared to the 10-year risk since most trials of CVD risk factor interventions are based on at most 6 years' follow-up.[206] Once an individual's CVD risk is predicted to some degree of certainty, management can be tailored accordingly, such as with individualised preventative interventions (i.e. the provision of specific dietary advice or encouragement of intensive physical activity). In addition, it can also help assess when specific drugs should be prescribed to control CVD risk factors,[207] The stratification of CVD risk in diabetic patients is of high importance since these individuals have an increased risk of CVD and recent reviews have supported the need for a multivariate approach. This is important for planning preventative measures in this type of risky population,[208]

It is necessary to predict an individual's CVD risk in order to plan for the management of elevated risk factors, with or without pharmacological therapy.[207] For example, recent studies do not support the use of preventative therapies (e.g. statins or aspirin) when the use of these treatments is not based on CVD risk estimation. Indeed, two meta-analyses,[209,210] and a subsequent individual study,[211] have shown that statin use increases the risk of hyperglycaemia which adversely affects the outcomes of glucose-lowering strategies if used without considering CVD risk. This is particularly important for low-risk patients who may not derive any cardiovascular benefits from the therapy. In addition, clinical trials on aspirin use do not support its use in all diabetic patients for the primary prevention of CVD.[212–214] Moreover, recent standards of care issued by the American Diabetes Association have suggested that the use of aspirin for CVD primary prevention in diabetic

patients should be based on risk estimation.[215] In fact, there has been a gradual shift in diabetes management from a glycaemic to an intensive multifactorial focus targeting reduction in the risk of major diabetic complications, thus emphasising the use of a multivariate approach to CVD risk stratification and subsequent management.[216,217] As such, various guidelines for the management of type 2 DM have advocated for the calculation of CVD risk in this vulnerable population in order to plan appropriate preventative and treatment strategies, including the use of anti-hypertensive, anti-platelet and anti-lipid drugs.[6,7]

Consequently, many different risk assessment tools in the form of statistical equations or risk charts have been developed in different parts of the world to estimate CVD risk among different types of populations. However, only two types of risk assessment tools are useful for estimating CVD risk in type 2 diabetic patients: those developed for general populations which consider type 2 diabetes as a risk factor, and those developed specifically for type 2 diabetic populations.

2.5.2 CVD risk assessment tools in general populations, considering diabetes as a risk factors

Many CVD risk assessment tools have been developed for the general population, although these vary in methodology and validity. For the purpose of this section, only the most common CVD tools developed for general populations with the following characteristics are discussed: 1) those that consider type 2 DM as a risk factor; 2) those that utilise CVD as a general outcome or at least include CHD (as the most common form of CVD) in the outcome; and 3) those derived from large mixed gender cohorts. These include the Framingham Heart Study (FHS) model, the Prospective Cardiovascular Münster Score (PROCAM-2007) model, the World Health Organization (WHO)/International Society of Hypertension (ISH) risk prediction charts, the Chinese Total CHD Risk Score, the Scottish Heart Health Extended Cohort risk score (also known as the Assessing Cardiovascular Risk Using SIGN Guidelines score), the Framingham General CVD (FG-CVD) Risk Profile for use in primary care, the Japanese

Cardiovascular Risk Model and the two latest versions of CVD risk score based on the British QResearch® database.[8,207]

The FHS and PROCAM-2007 models are among those recommended by certain professional guidelines in order to estimate CVD risk in diabetic patients. In this context, the FHS model is recommended by the guidelines of the European Society of Cardiology, European Association for the Study of Diabetes and the Australian National Vascular Disease Prevention Alliance, while the PROCAM-2007 model is recommended by the Canadian Diabetes Association.[8] Table 2.2 illustrates the important features of the studies which led to the development of these and other tools.[8,207,218] Many other tools are not discussed here because they either have not included type 2 diabetes as a risk factor, are specific for a population subgroup (e.g. a specific gender, age group or condition, such as patients with chest pain), have not included CHD among their outcome measures or only included fatal events, have been derived from studies with small sample sizes or are less commonly discussed in the literature.

Table 2.2: Global CVD risk prediction models developed for general adult populations which consider type 2 diabetes as a risk factor

Name of model (year)	Country (sample size)	Risk factors included in model	Study type and follow-up	Validation status in a diabetic population
FHS model[221] (1998)	U.S. (5,345)	Gender, age, DM, SBP, smoking, total cholesterol, LDL levels and HDL levels	Prospective community-based cohort study with 12 years of follow-up	Validated by many studies[12,219,220]
WHO/ISH risk prediction charts[222] (2003)	Different charts for different WHO regions	Age, gender, SBP, total cholesterol, HDL levels and smoking, with separate charts for	Population-based statistics (no original study data)	Not validated

	(not available)	DM		
PROCAM model[182] (2007)	Germany (26,975 for CHD tool and 8,130 for stroke tool)	Age, SBP, LDL levels, HDL levels, TG levels, smoking, DM and a family history of CHD	Prospective cohort study with 12 ± 6 years of follow-up	Not validated
Chinese adult CHD risk tool[181] (2006)	China (9,903)	Age, gender, DM, SBP, LDL levels, HDL levels and smoking	Prospective population-based cohort study with a mean follow-up period of 15.1 years	Not validated
ASSIGN model[188] (2007)	Scotland (13,297)	Age, gender, DM, SBP, smoking, total cholesterol or LDL levels, HDL levels, a family history of CVD and social deprivation	Prospective population-based cohort study with 10–21 years of follow-up	Not validated
QRISK2[180] (2008)	U.K. (1,535,583)	Age, gender, DM, SBP, ethnicity, smoking, total cholesterol/HDL ratio, BMI, a family history of CAD, social deprivation, current anti-hypertensive medications, atrial fibrillation and rheumatoid arthritis	Prospective open cohort study using general practice attendees with a mean of 7.3 years of follow-up for men and 6.9 years for women	Not validated

FG-CVD Risk Profile for use in primary care[177] (2008)	U.S (8,491)	Age, gender, DM, SBP, smoking, total cholesterol or LDL levels, HDL levels and treated BP	Prospective community-based cohort study with 12 years of follow-up	Validated in several studies involving different diabetic populations[13,14]
Japanese Cardiovasc-ular Risk Model[223] (2009)	Japan (1,756)	Age, SBP, serum total cholesterol, BM, current smoking status, DM and gender	Population-based prospective cohort study with 14 years of follow-up	Not validated
New QRISK[179] (2010)	U.K. (2,343,759)	Age, gender, smoking status, ethnic group, SBP, ratio of total cholesterol to HDL level, BMI, a family history of CHD, social deprivation, treated HTN, rheumatoid arthritis, chronic renal disease, DM and atrial fibrillation	Prospective open cohort study of routinely collected data in general practice settings with a maximum follow-up period of 16 years	Not validated

Abbreviations: FHS, Framingham Heart Study; DM, diabetes mellitus; SBP, systolic blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CHD, coronary heart disease; PROCAM, Prospective Cardiovascular Münster Score; TG, triglyceride; ASSIGN, Assessing Cardiovascular Risk Using SIGN Guidelines; CVD, cardiovascular disease; BMI, body mass index; CAD, coronary artery disease; FG-CVD, Framingham General CVD; BP, blood pressure; HTN, hypertension.

In summary, most of these tools are derived from studies among American or European populations. The included age range for most of the derivation cohorts was 30–74 years old. The risk tools differ in many ways and are presented in various formats, including charts, calculators and computing

programs.[23] The studies also differ in the outcomes used at endpoint. In this regard, some studies used CHD, while others used CVD or myocardial infarctions as endpoint outcomes. Additionally, the outcomes also differ in terms of including fatal events. Furthermore, these tools differ in their methodologies including the characteristics of the study sample, sample size (ranging from 1,756 to more than 2 million) study setting, time frame of follow-up, statistical analysis and included predictors.[8–10,23,207,218]

In addition, most of these tools were derived from original longitudinal studies, except for the WHO/ISH risk prediction charts, which were derived using databases related to prevalence rates of CVD risk factors and events in the corresponding regions. Most of the prediction models predicted the five- or 10-year risk using an average of eight predictors via Cox regression, logistic regression or Weibull proportional hazards modelling. The most commonly used predictors in most of these tools are traditional risk factors including age, gender, systolic blood pressure, smoking and cholesterol measurements as well as type 2 DM status.[8–10,23,207,218] Although some tools included a few non-traditional predictors, the value of their inclusion is thought to be low, as suggested by recent reviews.[9,224] In addition, recommendations from the U.S. Preventive Services Task Force concludes that current evidence is insufficient to assess the usefulness of using non-traditional risk factors in the assessment of CVD risk.[225]

2.5.3 CVD risk assessment tools specifically developed for type 2 diabetic populations

Many specific type 2 diabetes tools have started to emerge over the last two decades, due to the suggestion that diabetes-specific risk tools perform better than risk tools developed for the general population.[9,226] In this regard, the most common ones used to estimate CVD risk in type 2 diabetic populations—which use CVD as a general outcome or at least include CHD in the outcome—and that were derived from large cohorts with both genders include: the ADVANCE study model, the New Zealand Diabetes Cohort Study (DCS) model, the Australian FDS model, the SNDR equation, the Chinese Total CHD Risk Score, the Diabetes Audit and Research in Tayside, Scotland

(DARTS) study model, the U.S. Atherosclerosis Risk in Communities (ARIC) model and the UKPDS risk engine for diabetes patients.[8–10]
Overall, the UKPDS risk engine is the most commonly recommended model in professional guidelines, including the Canadian Diabetes Association, the Australian National Vascular Disease Prevention Alliance, the National Institute for Health and Clinical Excellence and the IDF.[8] Table 2.3 summarises the most important features of the aforementioned models.

Table 2.3: CVD risk prediction models specifically developed for patients with type 2 diabetes

Name of model (year)	Country (sample size)	Risk factors included	Study type and follow-up	Validation status in a diabetic population
ADVA-NCE model[141] (2011)	20 countries from Australasia, Asia, Europe and North America (7,168)	Age at diagnosis, gender, known DM duration, pulse pressure, retinopathy, atrial fibrillation, HbA1c, urine albumin/ creatinine ratio, non-HDL cholesterol level and treated HTN	Observational longitudinal study of a sample involved in a clinical trial with 4.5 years of follow-up	Validated using a separate sample involved in another clinical trial[141]
DCS model[101] (2010)	New Zealand (36,127)	Age at diagnosis, DM duration, gender, SBP, smoking status, total cholesterol-to-HDL ratio, ethnicity, HbA1c and urine albumin-to-creatinine ratio	Observational longitudinal study using primary care data with a median follow-up period of 3.9 years	Validated using a separate sample from the same population and in another sample from New Zealand[101,227]
FDS model[102]	Australia (1,240)	Age, gender, prior CVD event, urinary	Community-based	Validated using a

(2010)		albumin-to-creatinine ratio, HbA1c, HDL-to-cholesterol ratio and ethnicity (Southern European vs. Aboriginal)	longitudinal observational study with a mean follow-up period of 4.5 years (range: 0.6–5 years)	separate sample from the same population used for the derivation of the model[102]
SNDR model[145] (2008)	Sweden (11,646)	HbA1c, age at DM diagnosis, DM duration, gender, smoking, SBP, BMI and use of anti-hypertensive and lipid-reducing drugs	Longitudinal study using the diabetes registry database with a mean follow-up period of 5.6 years	Internal validation only
Chinese Total CHD Risk Score[103] (2008)	China (3,521)	Age, gender, current smoking status, GFR, DM duration and non-HDL cholesterol	Observational longitudinal study using a hospital-based diabetes registry with a median follow-up period of 5.40 years	Internal validation only
DARTS model[144] (2006)	Scotland (4,569)	Age at DM diagnosis, DM duration, HbA1c, smoking status, gender, SBP, treated HTN, total cholesterol and height	Population-based longitudinal study with median and maximum follow-up periods of 4.1 and of 9.5 years, respectively	Validated using a separate sample from England[144]

ARIC model[142] (2003)	U.S. (1,500)	Age, race, total cholesterol and HDL levels, SBP, Anti-hypertensive treatment and smoking status with and without BMI, waist-to-hip ratio, Keys dietary score, serum albumin and creatinine, factor VIII, white blood cell count and left ventricular hypertrophy	Community-based observational longitudinal study with a median follow-up period of 10.2 years	Not validated
UKPDS risk engine[146] (2001)	U.K. (4,540)	Age at DM diagnosis, gender, ethnicity (Afro-Caribbean vs. Caucasian-Indian Asian), current smoking status, HbA1c, SBP and HDL-to-cholesterol ratio	Observational longitudinal study of a sample involved in the UKPDS trial with a median follow-up period of 10.3 years	Validated in many studies involving different populations[12,13,228]

Abbreviations: ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; HDL, high-density lipoprotein; HTN, hypertension; DCS, Diabetes Cohort Study; SBP, systolic blood pressure; FDS, Fremantle Diabetes Study; CVD, cardiovascular disease; SNDR, Swedish National Diabetes Register; BMI, body mass index; GFR, glomerular filtration rate; DARTS, Diabetes Audit and Research in Tayside, Scotland; UKPDS, U.K. Prospective Diabetes Study.

Similar to the tools derived from general populations, most of the diabetes-specific tools were developed based on American and European populations; very few are based on eastern Asian populations. The studies differed in

terms of their statistical analyses, for example by using Cox regression, logistic regression and Weibull or Gompertz modelling methods. Moreover, the diabetes-specific tools differed in the sample sizes used (ranging from approximately 1,000 to 36,127 patients). Most of the tools were derived using data from type 2 DM cases, with only the UKPDS tool derived using newly diagnosed patients. The majority of the models predict the five-year risk of CVD with an average of eight predictors. The most commonly included predictors in these models are age, gender, DM duration, HbA1c, lipid-related entities, micro-albuminuria and smoking status.

Although some of tools included non-traditional CVD risk factors, the value of adding such predictors is thought to be low, as mentioned previously.[9,224] For example, in the ADVANCE model, non-traditional risk factors contributed little to the accuracy of CVD risk assessment when included along with traditional risk factors. In addition, apart from the ADVANCE model, lifestyle-related risk factors such as dietary patterns and physical inactivity are not included in any of the tools due to the difficulty in assessing and quantifying such factors, especially in studies involving reviews of patient records.[23]

Through critically reviewing the different risk assessment tools discussed above, the following major points are raised.

2.5.4 Suitability of applying general population risk tools to type 2 diabetic populations

Firstly, as these tools were developed primarily for the general population, they are not specific for type 2 DM populations. Secondly, most of the tools were developed for Western populations (primarily European and U.S. populations), with very few developed for East Asian populations and none at all derived for Arab populations. Despite similarities between populations in which existing models have been derived, developing a model specifically for a unique population is a common rationale for developing different models. This is due to variations in genetic and demographic characteristics as well as cultures and lifestyle patterns among different ethnicities and populations.

Thirdly, these tools do not include important traditional risk factors like HbA1c, DM duration and microalbuminuria.[9,11]

Most importantly, only two of the discussed general population tools, the FHS and FG-CVD Risk Profile models, were validated externally in diabetic populations. In particular, the FHS model is the most commonly cited and externally validated.[229] However, validation of the FHS and FG-CVD Risk Profile models have demonstrated significant underestimation and overestimation of CVD risk in certain cases, when used among samples of diabetic patients.[12–14] In addition, the external validation studies were conducted on European, Australian and other non-Arabian populations. In fact, some of the risk assessment tools were derived from studies performed in the 1970s and 1980s which may limit the generalisability of these tools, even in populations with similar ethnicities to the model derivation samples. This is because there was a high incidence of CVD events and diabetes during the 1970s and 1980s, which may have resulted in a tendency to over-predict current risk.[23] Furthermore, some tools were derived using logistic regression methods; however, Cox proportional hazards modelling is preferred in the derivation of risk models as it incorporates the time CVD events take to occur.[23]

2.5.5 Suitability of applying diabetes-specific risk tools to different diabetic populations

Although diabetes-specific risk models do overcome some of the disadvantages of tools developed for the general population and hence seemingly perform better in diabetic populations,[226] some limitations to these models still exist. Firstly, as with general population models, these tools have primarily been developed for Western populations (mainly European and U.S. populations) where Caucasian and African ethnicities predominate. As such, very few have been derived for Eastern Asian populations and none have been derived for Arabian populations. As concluded in several recent reviews, due to the complex relationship between diabetes-related complications and the geographical location of the patient and their environmental and lifestyle characteristics, CVD risk assessment models derived from specific diabetic

samples may not be suitable and hence not applicable to other diabetic populations.[10,23]

Secondly, certain traditional risk factors such as HbA1c and microalbuminuria are not included in some models, such as the Chinese Total CHD Risk Score. Also, DM duration is not included in several tools such as the ARIC and Australian FDS models and smoking is not included in the ADVANCE model. Notably, the ADVANCE model was derived from a sample of diabetic patients of 55 years and older who were involved in a clinical trial to assess the effect of specific anti-hypertensive and anti-diabetic drugs.

Thirdly, with regards to their external applicability, only the UKPDS Risk Engine and the ADVANCE, DCS and DARTS models were externally validated using different diabetic populations; however, external validation of the UKPDS Risk Engine on British, European, and Australian diabetic samples indicated significant risk overestimation.[12,13,228] In addition, the ADVANCE model was validated using participants involved in a randomised trial in which the potential influence of randomised treatments may have affected the performance of the tool.[141] Although the Scottish DARTS and New Zealand DCS models performed well in single validation studies, the models were validated using diabetic samples from England and New Zealand, respectively—populations which share the same ethnicity and lifestyle patterns as the samples used to derive the risk tools in the first place.[144,227] This is likely the reason behind their satisfactory performance.

In fact, none of the diabetes-specific tools have been validated in an Arabian population. Therefore, external validation studies for these tools in such populations are required. However, the results are not expected to differ from those showing poor performance during external validation. Additionally, the lengthy time lag between the development of some of these tools and the present, along with major advances in clinical practice, cast doubt on the validity of applying these risk tools even among populations of similar ethnicities. Moreover, nutrition habits and other lifestyle patterns have changed over time and differ according to location and culture; these factor

may further influence the validity of applying external tools to different populations.[10]

2.6 Status and studies related to CVD risk assessment tools in Oman

As previously mentioned, derivative studies to develop CVD risk assessment tools have not yet been conducted among either the Omani general or diabetic populations. In fact, a literature review revealed no studies of this kind among any type of Arabian population sharing similar characteristics. Therefore, due to the lack of local CVD risk tools, the use of an external risk prediction tool is necessary in local clinical settings for the sake of disease management. To this end, the Department of Non-Communicable Disease Control of the Ministry of Health in Oman has encouraged the use of the WHO/ISH risk prediction charts designed for patients in the Eastern Mediterranean region; these have been widely distributed in primary care institutions in Oman.[230,231] However, actual use of these charts by diabetes care physicians working in these institutions is thought to be rare and most physicians utilise their clinical judgment of CVD risk to plan patient management strategies.[230] This can be explained partially by a lack of knowledge among these physicians regarding the importance of such risk assessment tools and their clinical implications.[230]

Two comparison (non-validation) studies conducted in Oman have compared few existing CVD risk assessment models with the WHO/ISH risk prediction charts. In one study, the FG-CVD Risk Tool was found to overestimate the CVD risk in comparison to the WHO/ISH risk prediction charts, with important clinical differences in predicting CVD risk when the model was applied to a sample of Omani type 2 diabetic patients. The results from this study cast major doubts on the suitability of both of these tools for predicting actual risk among the Omani diabetic population.[24] In addition, the FG-CVD Risk Tool identified a greater proportion of patients at risk of developing CVD in a 10-year period compared with the WHO/ISH risk prediction charts. This difference was especially marked among patients with an intermediate risk of

CVD. Also, the FG-CVD Risk Tool identified almost double the number of men eligible for aspirin treatment at a 10% CVD risk threshold as compared to the WHO/ISH risk prediction charts (86% vs. 43%, respectively); among women, these proportions were 66% and 45%, respectively. For statins, the proportions of patients identified as suitable for treatment were 60% and 37% for men and 28% and 36% for women using the FG-CVD Risk Tool and WHO/ISH risk prediction charts, respectively. Although the study concluded that the FG-CVD Risk Tool tended to overestimate CVD risk and the number of patients eligible for primary CVD prevention in comparison with the WHO/ISH risk prediction charts, it is difficult to ascertain which tool reflects the actual situation since neither tool is specific to the Omani population.[24] In addition, a more recent study involving Omani diabetics predicted an increasing 10-year CVD risk over a 17-year period using three popular risk assessment tools, including the WHO/ISH risk prediction charts. The results of this study also identified discrepancies in the estimated risk according to each of the three tools. However, the study was not designed to validate each of the three tools, nor to compare the results between them.[232]

In brief, the existing risk assessment models are not always applicable to different populations.[10,23] However, the applicability of external CVD risk assessment tools among the Omani type 2 diabetic population and the need for a specific model for this population are elaborated in the following section which is presented as a published review article in relation to this thesis work.

2.7 Applicability of the existing CVD risk assessment tools to type 2 diabetics in Oman (Paper 1)

2.7.1 Introduction

This section includes a published review article to justify the importance of developing a risk assessment model specific to the type 2 diabetic population in Oman. As the applicability of existing global CVD risk models among Omani type 2 diabetics have not been previously addressed in the literature, this review aimed to touch upon this issue. The article commences with a summary of the existing global CVD risk tools that were discussed in detail in

the former part of this Chapter. Then, it focuses on the current use of available CVD risk assessment tools in local clinical settings in Oman and ends with a critical argument on the applicability of external CVD risk tools to the Omani type 2 diabetic population, emphasising the need for a more specific CVD risk assessment model for this particular population.

Notably, the format of this paper conforms to the formatting/style requirements of the *Oman Medical Journal*, which may not be consistent with those in other sections/chapters of this thesis. However, the pages, figures and tables are re-numbered to be consistent with the flow of the thesis. The bibliographic details of the co-authored paper, including all of the authors, are:

Al-Rawahi A, Lee P. Applicability of the Existing CVD Risk Assessment Tools to Type II Diabetics in Oman: A Review. Oman Med J. 2015 Sep;30(5):315–9. doi: 10.5001/omj.2015.65.

Declaration

I (the candidate) am the first and the corresponding author of this paper. My contribution to the paper involved: generating the idea, designing the research, reviewing the literature, critically compiling the evidence, drafting the manuscript and publishing the paper. This contribution is acknowledged by all co-authors.

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Applicability of the Existing CVD Risk Assessment Tools to Type II Diabetics in Oman: A Review

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2.7.2 Abstract

Patients with type 2 diabetes (T2DM) have an elevated risk for cardiovascular disease (CVD), and it is considered to be a leading cause of morbidity and premature mortality in these patients. Many traditional risk factors such as age, male sex, hypertension, dyslipidemia, glycemic control, diabetes duration, renal dysfunction, obesity and smoking have been studied and identified as independent factors for CVD. Quantifying the risk of CVD among diabetics using the common risk factors in order to plan the treatment and preventive measures is important in the management of these patients as recommended by many clinical guidelines. Therefore, several risk assessment tools have been developed in different parts of the world for this purpose. These include the tools that have been developed for general populations and considered T2DM as a risk factor, and the tools that have been developed for T2DM populations specifically. However, due to the differences in socio-demographic factors and lifestyle patterns, as well as the differences in the distribution of various CVD risk factors in different diabetic populations, the external applicability of these tools on different populations is questionable. This review aims to address the applicability of the existing CVD risk models to the Omani diabetic population.

Keywords: Cardiovascular Diseases; Type 2 Diabetes Mellitus; Risk Assessments; Arabs; Oman

Type 2 diabetics have an elevated risk for cardiovascular disease (CVD), estimated as being two-to-six fold higher compared to the general population.[1] CVD is also considered as a leading cause of morbidity and premature mortality in patients with type 2 diabetes.[2]

Many traditional risk factors such as age, male sex, hypertension, dyslipidemia, glycemic control, diabetes duration, renal dysfunction, obesity, smoking, and physical inactivity have been extensively studied and identified to be independent factors for CVD.[1,3] Recently, other non-traditional predictors such as erectile dysfunction, unhealthy diet, social deprivation and other inflammatory, hematological, and thrombogenic markers have been studied and showed a positive relationship with CVD among diabetics.[3,4] However, traditional risk factors have been found to explain between 75%–90% of CVD events.[5,6] Also, there is no sufficient evidence that routine monitoring of these factors leads to better diagnostic and therapeutic results in diabetic patients.[3,7]

2.7.3 CVD risk assessment tools

Risk assessment tools, in general, are mathematical models or charts used to estimate the risk of an outcome event in an individual. They use the predictive information available for the various risk factors of the specified condition using mathematical models. Usually such models are used for diagnostic and prognostic purposes. Diagnostic models estimate the current risk of a disease or health event and prognostic models estimate the future risk of a particular disease or health event within a given period.[8,9] CVD risk assessment tools estimate the CVD risk in an individual based on the information available mainly for the various traditional CVD risk factors.

Various professional guidelines for the management of type 2 diabetes mellitus (T2DM) recommend the use of CVD risk assessment tools to quantify the risk among patients with diabetes. This would also guide the initiation of appropriate preventive and treatment strategies, including antihypertensive, antiplatelet, and antilipids drugs.[10,11] Many different risk assessment tools were developed in different parts of the world in the past decades to assess the CVD risk among patients with T2DM. These include the tools developed

for general populations and considered T2DM as a risk factor, and the tools developed specifically for T2DM populations.

Tools for general populations, with diabetes as a risk factor

In general populations, many risk assessment tools have been developed that vary in their methodologies. Listed in Box 1 are the most common tools established to estimate the CVD risk in general populations that consider T2DM as a risk factor and use CVD as a general outcome or, at least, include coronary heart disease (CHD) in the outcome (as it is the most common among all CVD events) and were derived from large cohorts with both sexes.[12,13]

Box 1: Common tools established to estimate CVD risk in general population

- Framingham Heart Study (FHS) model.
- New Prospective Cardiovascular Munster Score (PROCAM-2007) model
- World Health Organization /International Society of Hypertension (WHO/ISH) charts
- Chinese Adult Cardiovascular Disease risk tool,
- The risk score based on the Scottish Heart Extended Cohort (also known as Assessing Cardiovascular Risk Using SIGN Guidelines (ASSIGN))
- Framingham General (FG) CVD risk profile for use in primary care
- Japanese cardiovascular risk model
- The two last versions of the Cardiovascular Disease Risk Score Based on the British QRESEARCH database (QRISK2 and the new QRISK)

The FHS model and the PROCAM model are recommended and incorporated by some of the professional guidelines to estimate the CVD risk in patients with diabetes. The FHS model is recommended by the European Society of Cardiology and European Association for Study of Diabetes Guidelines and

the Australian National Vascular Disease guidelines. The PROCAM model is recommended by the Canadian Diabetes Association guidelines.[13]

Notably, most of these tools were derived from studies among American or European populations. The age range for most of the study cohorts was 30–74 years. However, these tools differ in many ways and they are presented in various forms, including risk charts and electronic risk calculators .[14] The sample sizes ranged from 1,756 patients to more than two million patients. They also differ in the endpoint outcomes used, which include CHD, CVD, and myocardial infarction. Some outcomes also include fatal events. Furthermore, these tools differ in their methodologies including characteristics of the study sample, study setting, follow-up time frame, statistical analysis, and the included predictors.[12,17] Most tools were derived from original longitudinal studies except the WHO/ISH charts, which were derived using databases related to the prevalence of the common risk factors of CVD and CVD event rates in the corresponding WHO regions. Most of these prediction models predicted the five- or 10-year risk using an average of eight predictors through cox regression, logistic regression, or Weibull proportional hazards modeling. Age, sex, systolic blood pressure, smoking, cholesterol measurements, and T2DM status were the most commonly used predictors.[12-17] Some tools included non-traditional predictors, but the value of adding them was thought to be small.[16,18] In addition, recommendations from the US Preventive Services Task Force concluded that the current evidence was insufficient to assess the usefulness of including the non-traditional risk factors in the risk assessment.[19]

Tools specific for type II diabetic populations

Many specific T2DM tools have emerged in recent years due to the suggestion that diabetes-specific risk tools perform better than those developed for the general population.[16,20] The most common ones established to estimate CVD risk in the T2DM population that take CVD as a general outcome or include CHD in the outcome and were derived from large cohorts with both sexes are given in Box 2.[13,15,16] Generally, the UKPDS risk engine is the most commonly recommended model by professional guidelines

including the Canadian Diabetes Association, the Australian National Vascular Disease Prevention Alliance, the National Institute for Health and Clinical Excellence and the International Diabetes Federation.[13]

Box 2: Common tools established to estimate CVD risk in the type II diabetic population.

- Action in Diabetes and Vascular Disease, the Preterax and Diamicron-Controlled Evaluation (ADVANCE) study model.	MR
- New Zealand Diabetes Cohort Study (DCS) model.	
- Australian Fremantle Diabetes Study (FDS) model.	
- Swedish National Diabetes Register (SNDR) equation.	
- Chinese Total CHD risk score.	
- Scottish Diabetes Audit and Research in Tayside, Scotland (DARTS) database model.	
- U.S Atherosclerosis Risk in Communities (ARIC) model.	
- U.K Prospective Diabetes Study (UKPDS) risk engine model	

Like the tools derived from the general population, most of the diabetes-specific tools were developed based on American and European populations and very few were based on Eastern Asian populations. These tools differ in the study sample sizes, which range from more than 1,000 to more than 35,000 patients. Most were derived using prevalent T2DM cases and only the UKPDS tool was derived using newly diagnosed diabetic patients. The majority of the models predict five-year risk with an average of eight predictors. The most commonly used predictors in these models are age, sex, diabetes duration, glycated hemoglobin levels, lipid-related entities, microalbuminuria, and smoking. Again, some tools have tried to include non-traditional factors, but the value of adding them is thought to be small.[16,18] The studies also differed in their statistical analysis methods similarly to the tools developed for the general population.

2.7.4 CVD risk assessment in Oman

T2DM and its complications have imposed a considerable burden in Oman. Three consecutive epidemiological surveys have shown a gradual increase in the prevalence of T2DM from 10% to 12.3% over 17 years.[21-24] It is estimated that by 2050 there will be around 350,000 people with T2DM living in Oman. [25] Moreover, a hospital based study showed that more than half of the Omani patients who presented for coronary artery bypass surgery had diabetes.[26] Additionally, related data showed a high prevalence of CVD traditional risk factors among Omanis.[24,27,28] Therefore, the growing trend of T2DM and CVD risk factors inevitably makes the problem of CVD challenging to the Oman healthcare system.

To date, no risk assessment tool derivative studies have been conducted in any Arab countries, including Oman. Therefore, the use of external risk assessment tools is encouraged in the clinical setting, at least for the time being, for the sake of disease management. The Department of Non-Communicable Disease Control (NCDC) has encouraged the use of the WHO/ISH EMRO-B charts designed for patients in the Eastern Mediterranean region (as Oman is part of this region) and these have been widely distributed in primary care institutions.[29,30] However, the use of these charts in diabetes care is thought to be rare. This lack of use can be explained partially by the lack of knowledge about the importance of such risk assessment tools and their clinical implications.[29]

In the Arab world, no studies were found related to testing the validity of the existing CVD risk tools on diabetic populations apart from one comparison study conducted in Oman. In this study, the FG-CVD risk model was observed to overestimate the CVD risk compared to the WHO/ISH risk charts when applied to a sample of Omani patients with T2DM.[31] For example, the GF-CVD tool identified a higher proportion of patients compared to the WHO/ISH tool at 10-year CVD risk especially in the intermediate risk group of patients. The GF-CVD tool identified almost double the number of men eligible for aspirin treatment at CVD risk thresholds of 10% compared to the WHO/ISH charts (86% vs. 43% respectively). In women, the proportions were 66% and

45%, respectively. For statins, the figures were 60% and 37% for men and 28% and 36% for women, respectively. This means that if the GF-CVD risk tool was applied in the Oman health setting, the diabetes care costs would sharply increase.

2.7.5 Critical arguments on the application of the existing tools

The tools that were primarily derived for general populations are not specific for T2DM populations, which carry a higher risk. In addition, these tools have not included important risk factors like glycemic control, diabetes duration, and micro-albuminuria.[16,32] Moreover, most of the two types of tools have been derived from western populations (European and US populations) and very few have been derived from East Asian populations. Only a few tools were validated externally on diabetic populations and these studies demonstrated poor performance of these tools when applied to diabetic patients. [33-35] Also, the external validation studies were conducted on European, Australian and other populations, which share similar ethnicities and lifestyles with the populations used to develop these tools.

The differences in sociodemographic factors, culture, lifestyle, and the distribution of various CVD risk factors and CVD occurrence in those populations should be considered in the application of such tools in different populations. Despite the similarities between the populations for which existing models were derived, developing a model specific for each unique population is a common rationale mentioned in the studies that gave rise to the current models. In fact, due to the strong relationship between diabetes and its complications with the patient's geographical location and environmental and lifestyle characteristics, the existing risk models are not always applicable to different populations. Therefore, it is better for each particular population to have its own risk assessment tool.[14,15] Additionally, the time since some of these tools were derived and the major differences in the clinical practices nowadays lead us to question the validity of applying these risk tools even in populations with similar ethnicities.[15]

The existing tools have not been validated in any Arab population including Omanis. However, as mentioned before, external validations in non-Arab

patients with diabetes have shown a poor performance of these tools.[33-35] The single study conducted in Oman, comparing the FG-CVD risk tool to the WHO/ISH charts currently used, has shown significant discrepancies in the risk assessment results between the two tools when applied to a sample of Omani patients with T2DM. Although the study concluded that the GF-CVD tool overestimated the risk and the number of patients eligible for primary prevention of CVD compared to the joint WHO/ISH charts, it is difficult to judge which one is more relevant and closer to the real situation as both tools are not Omani-specific.[31]

Moreover, the WHO/ISH risk charts were not derived from original studies, but derived using databases related to prevalence of the CVD risk factors and CVD event rates for the Eastern Mediterranean region. Although this region includes Arab populations mostly, it also includes a non-Arab population (Iranians). Therefore, these charts are not that specific. Additionally, these charts have not included other important risk factors related to patients with diabetes, like glycosylated hemoglobin and diabetes duration.

Therefore, due to the above limitations, physicians may be faced with uncertainties in the CVD risk estimation using these external tools. This, in turn, may affect the clinical management of diabetic patients and the costs of the diabetes care.

2.7.6 Conclusion

The applicability and accuracy of the existing CVD risk tools for local populations is questionable since these tools are not considered the optimal ones to be applied in different populations. It seems that there is a need for a population-specific risk assessment tool for Omani patients with T2DM to monitor their CVD risk and inform future treatment and case management strategies.

Disclosure

The authors declared no conflict of interest.

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Chapter 3: Research Methodology

3.1 Introduction

Chapter 2 presented background information of the current situation and burden of cardiovascular disease (CVD) both globally and in Oman. It also provided a detailed review of the literature related to existing global CVD risk assessment tools and their application among different populations. In addition, it elaborated on the gap in the application of these tools to Omani type 2 diabetics and addressed the crucial need for a more specific tool for this population. This chapter presents a methodological plan of this research in order to answer the research questions and develop a CVD risk assessment model suitable for the Omani population. It includes the conceptual framework of the project, the study design used, the target population and the sampling method of this study. It also presents the data collection methods and instruments and provides variable definitions, issues related to data quality and management and detailed data analysis methods. In addition, details on measurements and ethical considerations are provided.

3.2 Conceptual framework

The conceptual framework of this study is illustrated in Figure 3.1. The research project began by seeking to gain an overall understanding of CVD-related factors from a global perspective and the existing models/tools available to assess CVD risk among diabetic populations. The literature review suggested that CVD incidence and patterns of CVD risk factors differ according to population; therefore, these differences should be taken into consideration in the development and application of any new CVD risk assessment model. As a result, CVD incidence in Oman and patterns of CVD risk factors among Omani diabetics have to be explored and compared to global figures. As suggested in the previous chapter, developing a specific CVD risk assessment model for Omani diabetic patients is necessary. The second part of the conceptual framework describes the steps required to develop a suitable CVD risk assessment model for this particular population.

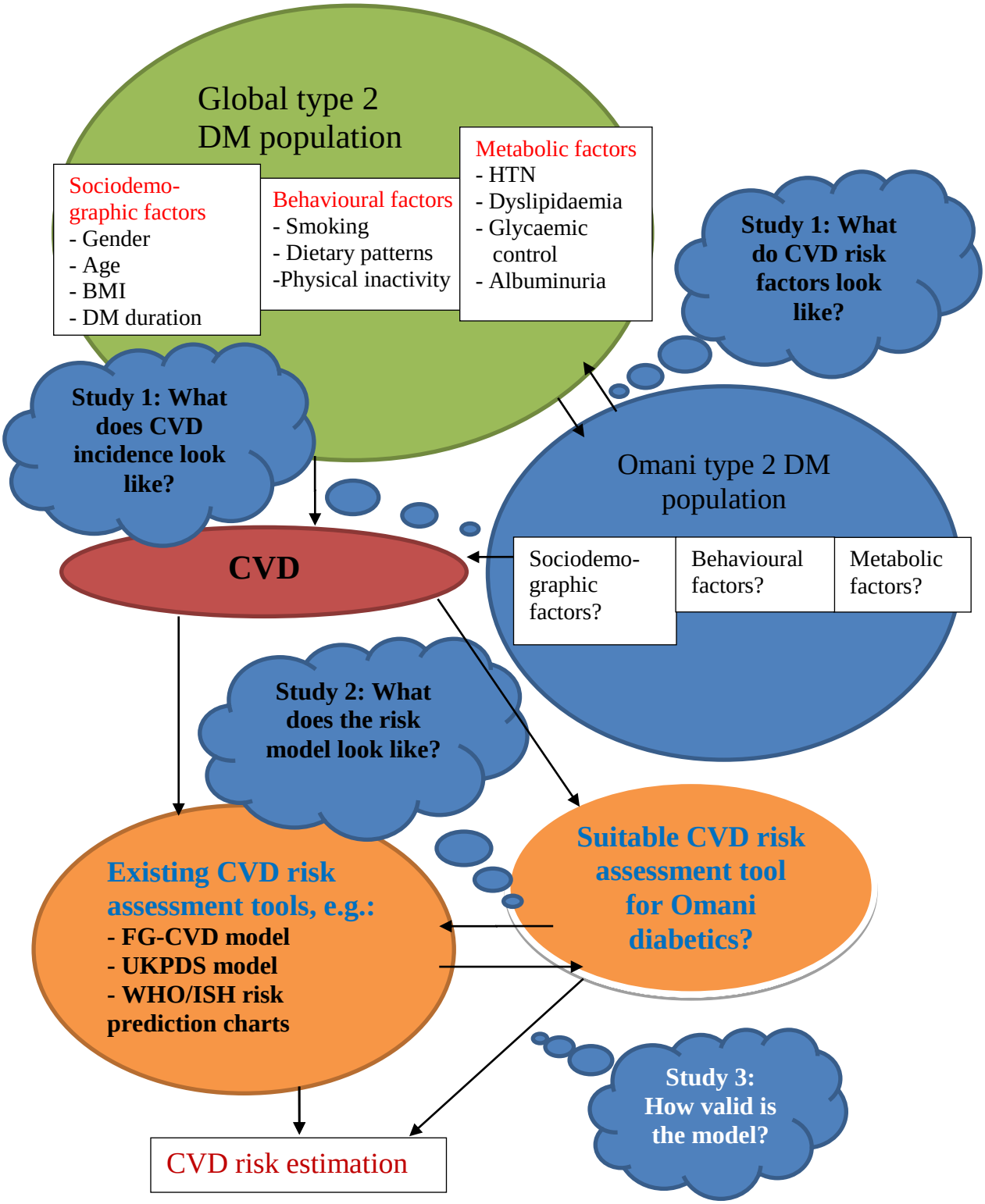

Figure 3.1

The conceptual framework of the study

Abbreviations: DM, diabetes mellitus; BMI, body mass index; HTN, hypertension; CVD, cardiovascular disease; FG-CVD, Framingham General CVD; UKPDS, U.K. Prospective Diabetes Study; WHO, World Health Organization; ISH, International Society of Hypertension.

However, testing the validity of the developed model is crucial to ascertain the applicability of the developed model to Omani diabetics. As per the objectives of this thesis, the overall fieldwork was completed through three sub-studies. The first explored CVD incidence and risk factor patterns among the target population. This study was the first attempt in establishing CVD incidence among Omani diabetics. Also, it provided preliminary results regarding the CVD-associated risk factors. The associated risk factors identified in the first study were carried over to the second study. The second study aimed to develop a CVD risk prediction model for the target population. This was followed by the third study which was established to validate the accuracy of the model in a separate sample selected from the same target population.

3.3 Study design

All of the three sub-studies utilised an observational longitudinal study design, in which a diabetic cohort was chosen from a database of registered patients with medical records starting from baseline in 2009–2010 until the end-point. The end-point included CVD event or death (both CVD and non-CVD deaths) until the end of the data collection period in December 2015. However, at data analysis stage, the whole cohort was processed as per the framework of a retrospective cohort study in which the cohort was split into exposed and unexposed groups based on identified key risk factors.

An observational longitudinal study involves following up participants within a cohort from baseline onwards. This design is particularly useful for assessing disease aetiology and prognosis, which are useful for clinical decision-making.[233] Unlike cross-sectional and the classical case-control studies, a retrospective cohort study can provide stronger evidence concerning causal relationships because it considers the temporality between exposure and outcome. In other words, the researcher can be certain that the exposure precedes the outcome.[234] Although prospective cohort and prospective nested case-control studies usually yields better quality of data, these are much more expensive and time consuming. On the other hand, retrospective nested case-control study does not yield better evidence compared to retrospective cohort study since it is retrospective in nature. In addition, nested case-control

studies usually utilise a subset of non-disease subjects in the cohort to form the control group, while in retrospective cohort studies all the non-disease subjects in the cohort are utilised to form the control group, allowing a better representative sample. Furthermore, the studied outcome (CVD) in this project is not rare, making cohort study design feasible. For this project, the year 2009–2010 was chosen as the baseline point so that the minimum follow-up period until the end of the data collection period in December 2015 would be five years.

3.4 Study setting and target population

The reference population for this research project included the Omani type 2 diabetic population residing in the catchment areas of all primary care institutions (health centres and polyclinics) in the Aldakhiliyah Province of Oman. This region was chosen as the researcher had relatively easy access to the necessary data after having been invited to conduct this research by the Department of Non-Communicable Disease Control in this region. Also, the involved institutions were geographically close to each other, making it easier for the candidate to coordinate fieldwork activities. Other provinces in Oman were not involved due to limited time and resources.

The Aldakhiliyah Province is one of the biggest provinces in Oman, with an area of 309.5 thousand km^2 and a total of 298,574 Omani inhabitants.[83,84] Health services in this region include 25 primary care institutions (including 21 health centres and four polyclinics) as well as four local hospitals and one main tertiary hospital.[83] Each primary care institution serves all patients residing within its catchment area; however, the four polyclinics (the Nizwa, Sumail, Bahla and Izki Polyclinics) serve larger catchment areas as compared to the health centres.

Diabetes care services in this region are delivered at both types of primary institutions (polyclinics and health centres), although 50% of patients receive their treatments and are followed up at the four polyclinics due to their larger catchment areas.[235] A diabetes mellitus (DM) diagnosis is made according to the World Health Organization (WHO) criteria in all of these institutions. All

diagnosed patients are registered in the National Diabetes Register and regularly followed up for disease management at intervals ranging from monthly to every three months, depending on their disease conditions. Annual check-ups for diabetes-related complications and an assessment of CVD risk factors are mandatory for each patient. As per the guidelines of the local diabetes control programme, all patients are comprehensively assessed at their first DM diagnosis and then re-assessed at least annually for main CVD risk factors and for diabetes-related complications (including CVD) using standardised assessment forms and following standardised diabetes follow-up procedures.[236,237]

All patient assessments at these institutions are administered by qualified diabetologists, trained general physicians and trained nursing staff. In addition, the Department of Non-Communicable Disease in the region supervises the delivery of assessments and follow-ups and provides the required training for related staff working in the diabetes clinics. All patient demographic and clinical data are entered and maintained in computerised patient records by the team members of the diabetes care clinics. In addition, patients with serious complications or emergencies like acute coronary heart disease (CHD) may be referred for further management to the tertiary care institutions within (Nizwa Hospital) or outside (e.g. Sultan Qaboos University Hospital and Royal Hospital) the province, where computerised medical records are also kept for further management.

Inclusion/exclusion criteria for the study population:
Several inclusion and exclusion criteria were applied to refine the study population in order to reduce selection bias. All initially included subjects were carefully selected using the inclusion/exclusion criteria of this study as listed below:

Inclusion criteria:

- Individuals of Omani nationality.

- Patients with confirmed diagnoses of type 2 DM whose clinical data was recorded in the National Diabetes Register as of 2010 or earlier.
- Patients who were free of CVD (CHD, stroke and PAD) at baseline.
- Patients with available follow-up data until end-point.

Exclusion criteria:

- Patients who developed CVD in the follow-up period due to causes other than CVD risk factors, including patients who developed non-ischaemic heart disease and those who underwent non-ischaemic-related limb amputations during the follow-up period.
- Patients with end-stage renal disease and liver cirrhosis.
- Patients with a large proportion of missing data regarding their risk factors or CVD outcomes at baseline.

3.5 Sampling methods and sample size

According to the Department of Non-Communicable Disease Control in Aldakhiliyah Province, a total of 7,599 type 2 diabetic patients were recorded within the National Diabetes Register in 2010 through all health institutions in the region; of these, over 50% of the patients were registered and followed-up by the four polyclinics.[235] As most diabetic patients were followed up at the four polyclinics rather than at the health centres, three main polyclinics (Nizwa, Bahla and Izki Polyclinics) and one large health centre (Manah Health Centre) were chosen for the sample selection necessary to study CVD incidence and risk factor patterns and to develop the CVD risk assessment model. These institutions were chosen as per the advice of the Department of Non-Communicable Disease Control in the region, since less missing data would be expected within these institutions as compared to the others. The total number of type 2 diabetic patients registered in these four institutions at the baseline was 3509.[235] Subsequently, eligible type 2 diabetic patients recorded in the National Diabetes Register by the selected four institutions in 2009–2010, who were free of CVD at baseline and who met the inclusion

criteria were included in this study. After applying the inclusion/exclusion criteria, a total of 2,039 patients were found to be eligible.

The minimally required sample size to estimate CVD risk (incidence) was calculated using a statistical formula designed for observational studies as below:[238]

$$\mathbf{N = \frac{Z^2 \times p \times (100 - p)}{d^2}}$$

Where;

- N = required sample size,
- Z = 1.96 constant value for a 95% confidence interval,
- p = estimated proportion (prevalence/incidence) of the outcome in the population, and
- d = desired margin of error / permissible error.

Using an estimated incidence from previous studies maximally reaching 18%,[101,239] a desired margin of error of 5% and a 95% confidence interval, the minimally required sample size (N) was calculated as follows:

$$\mathbf{N = \frac{1.96^2 \times 0.18 \times 0.82}{0.05^2} = 0.5670 / 0.0025 = 227} \text{ patients}$$

Considering an observational design, potential incomplete data and loss to follow-up, adding 50% for each of these considerations was deemed reasonable. Therefore, the required sample was:

227 x 150% x 150% x 150% = 767 patients

However, in order to minimise sampling error, all 2,039 eligible patients from the four institutions were included in this study in view of the available budget and resources. As such, the sample size of included DM patients to study CVD risk/incidence was much larger than required.

In the second sub-study, the same sample (2,039 patients) was utilised to derive a CVD risk model. However, patients with incomplete data related to any key risk factor at baseline were excluded from the Cox regression analysis. The sub-sample available for this multivariate analysis was therefore 1,314. The minimum sample size required for the proposed multivariate regression analysis depends on the number of predictors studied. Usually, 10 outcome events per variable is enough to draw a Cox regression model.[240] In this sub-study, 7 predictors were included in the regression analysis. Therefore, the required calculated number of CVD events was around 70, which was much less than the number of CVD events appeared in this cohort.

The third sub-study was designed to validate the developed CVD risk equation. A separate sample of type 2 diabetics from the same population and residing in the same province, but external to the previous sample used for model derivation, was needed. For this purpose, Samail Polyclinic and Burkat Almoz Health Centre were chosen for sample selection purposes. These two institutions were selected as they serve a relative large number of patients in comparison to the remaining health centres, and were expected to have a lower proportion of missing data. The total number of diabetic patients registered in the two institutions at baseline was 881.[235] Similar to the model derivation sampling procedures, the sampling frame for this sub-study included all type 2 diabetic patients recorded in the National Diabetes Register in 2009–2010 by the selected two institutions, who were free from CVD at baseline and were followed-up until end-point. After applying the same inclusion/exclusion criteria, a total of 405 patients were identified as eligible subjects with complete data related to key factors and CVD outcomes. All of these 405 DM patients were hence included in the validation study.

3.6 Data collection methods

This project made use of secondary data collected routinely by trained physicians and nursing staff working in the diabetes clinics of selected institutions. Demographic data (including gender, age, age at DM diagnosis, body mass index (BMI) and DM duration) and clinical data regarding the outcome and all key risk factors (including physician's clinical assessments

and laboratory tests) at baseline were obtained from the National Diabetes Registry System and computerised patient files at all selected health institutions. In addition, data related to the CVD outcomes at end-point were tracked throughout the entire follow-up period from baseline until the end of December 2015 using the same data sources as well as the computerised files of the same patients in other tertiary institutions (e.g. Nizwa Hospital, Sultan Qaboos University Hospital and Royal Hospital) when required.

Data related to baseline risk factors were retrieved manually by reviewing each patient's healthcare visits in 2009–2010 and CVD outcomes were identified by reviewing physicians' clinical notes and diagnoses for each patient during the follow-up period. Moreover, death certificates were also obtained to confirm all causes of death occurring during the study as documented by the attending physicians. Most patients were contacted telephonically by research assistants to confirm smoking status, family history of CVD patients and CVD outcome events.

The data were collected by 10 trained nursing staff working in the diabetes clinics of the selected institutions. All data were manually recorded using a well-designed data collection sheet (see appendix B). Proper training was delivered to all of the data collectors by the researcher prior to data collection. An initial one-week pilot period for data collectors was given to ensure their understanding and to ensure they possessed the required capabilities for completing the data collection tasks. In addition, regular monitoring of data collection was conducted by the researcher on a weekly basis to ensure the quality of data. Any queries arising during this phase were always discussed among the data collection team prior to being resolved.

3.7 Variable definitions and measurements

A CVD outcome was defined as the first fatal or non-fatal CHD, stroke or PAD event diagnosed by internal medicine physicians based on their clinical assessment and confirmed using diagnostic tests. All diagnostic tests were performed by qualified laboratory technicians and interpreted by specialised physicians at the included institutions. A CHD diagnosis included stable or

unstable angina and myocardial infarctions; this was confirmed by 12-lead electrocardiography (ECG) and a serum troponin test. However, patients for whom the diagnosis was unclear were referred to cardiologists in tertiary hospitals within or outside the province. In some cases, an ECG stress test (i.e. the treadmill test) and coronary angiography was needed to confirm the diagnosis. Episodes of stroke were confirmed by computed tomography while PAD was confirmed by a clinical diagnosis of gangrene, a limb amputation due to an ischaemic cause or clinical picture of ischemic limb confirmed by ankle-brachial pressure index and angiography.

The same diagnostic criteria were applied at baseline to ensure that the included participants were free from CVD at the beginning of the study. The diagnostic criteria for CHD, stroke and PAD are standardised across all institutions and are consistent with international guidelines.[114,127,241] In addition, as fatal events were included in CVD outcomes, causes of death were confirmed from death certificates and cross-checked from patient's records. Patients who died of non-CVD-related causes before the end-point event occurred were recorded as censored data, with various total follow-up durations in the study.

The variable definitions listed in Table 3.1 were used to assess CVD outcomes and various key risk factors according to the Diabetes Mellitus Management Guidelines for Primary Health Care Manual and the Operational and Management Guidelines for the National Non-Communicable Diseases Program of the Ministry of Health, Oman.[231,236] Risk factors were collected as continuous variables and were categorised using the cut-off points defined in the local guidelines, which is consistent with international guidelines.[231,236]

3.8 Data quality and management

All data were entered into a computer and managed using the Epi-Data entry software, in order to reduce entry errors. In addition, the following procedures were applied in order to ensure that the collected secondary data was of good quality and the created electronic files were secure:

- A proportion of the collected data (10%) was randomly chosen and rechecked with various medical records.
- A systematic data coding scheme was consistently used by the researcher and those involved with data collection and data entry.
- Data screening and cleaning were done prior to analysis to check for coding errors.
- Backup files and hard copies of the data were saved in other computers/filing cabinets to negate the possibility of data loss.
- Electronic data access was restricted to the research team only.
- All data would be archived after the completion of the project for at least five years.

Table 3.1: Variable definitions for CVD outcomes and key risk factors

Variable	**Definition and cut-off points**
CVD outcome	The first fatal or non-fatal CVD recorded event from the following list: • Confirmed physician diagnosis of CHD in the form of a stable angina, unstable angina or an acute myocardial infarction. • Confirmed physician diagnosis of ischaemic or haemorrhagic stroke. • Confirmed physician diagnosis of PAD (either an ischaemic-related limp, gangrene or amputation).
HTN	Physician diagnosis of HTN (SBP ≥140 mmHg or DBP ≥90 mmHg confirmed in BP chart readings after excluding other causes).
Dyslipidaemia	Defined as having at least one of the following lipid abnormalities as confirmed by a standardised laboratory test: • Total cholesterol ≥5.2 mmol/l. • LDL ≥2.6 mmol/l. • HDL ≤0.9 mmol/l for males and ≤1.3 for females. • TG level ≥1.7mmol/l.
Albuminuria	Defined as a persistent albumin/creatinine ratio of ≥2.5 in

(microalbuminuria or proteinuria)	males and ≥3.5 in females or a persistent protein/creatinine ratio of ≥ 45, confirmed at least twice within three months or more by a standardised laboratory test, after excluding other possible cause of proteinuria like infections or strenuous exercise.
Glycaemic control	Good, intermediate and poor glycaemic control was defined as HbA1c measurements of <7%, 7–8% and >8%, respectively, as confirmed by a standardised laboratory test.
Obesity	BMI was calculated as body weight/height in metres squared. Overweight was defined as a BMI of ≥25–30 kg/m^2 and obesity as BMI ≥30 kg/m^2. Weight and height were measured using standardised calibrated instruments.

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; PAD, peripheral arterial disease; HTN, hypertension; SPB, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; LDL, low-density lipoprotein; HDL, high-density lipoprotein; TG, triglyceride; HbA1c, glycosylated haemoglobin; BMI, body mass index.

3.9 Data analysis methods

The SPSS software, Version 22, was used for data analysis. In all three sub-studies, percentages with 95% confidence intervals (CIs) were calculated for the incidence and other important categorical variables as descriptive analysis. For continuous variables, means with standard deviations and medians were described. All continuous variables were categorised according to pre-defined clinical cut-off points as shown in Table 3.1. Chi-squared tests and independent sample T-tests were used in the three sub-studies to assess the crude differences between proportions and means, respectively, in relation to different risk factors and outcome status.

In the first sub-study, the data of the diabetic cohort was divided into exposed and unexposed groups based on key risk factors. The univariate relationship between CVD outcome and each of the key risk factors was assessed using Kaplan-Meier survival analysis, along with log-rank, Breslow and Tarone-Ware tests to compare survival distribution between groups. In addition, odds ratios with 95% CIs were computed using SPSS software to estimate relative

risk. Furthermore, an analysis of variance (ANOVA) test was used to assess the crude relationship between key continuous and categorical variables when required. A *P* value of < 0.05 was considered to indicate statistical significance.

Cox regression modelling was used in the second sub-study to identify independent CVD risk factors and to derive the final CVD risk assessment model in the form of a statistical equation. Log minus log (log – log) plots for categorical predictors of CVD were used to assess a possible time-varying effect to meet the proportional hazards assumption for using a Cox regression method. In addition, the model fit was tested by comparing changes in the -2 log likelihood statistic in the modelling process. Based on the Cox regression results, the t-year CVD probability equation was modelled using the baseline survival probability function $(S_0(t))$ and expressed as:
t-year CVD probability = $1 - S_0(t)^{Exp\sum XiBi}$, where $S_0(t)$ is the cumulative survival (probability of non-CVD) over t-years, $Exp \sum XiBi$ represents the cumulative hazard ratio, *Xi* represents the CVD-associated factors included in the model and *Bi* represents the factor coefficients in the model.[242,243]

In the third sub-study, the overall performance of the developed risk assessment model in the derivation and validation samples was assessed by comparing predicted mean CVD risk to observed mean risk in both samples. Areas under the receiver operating curves with 95% CIs were used to assess the ability of the model to discriminate between diabetics with and without CVD outcomes in both samples. Calibration of the model was assessed by comparing predicted mean risk to observed mean risk in fifths (quintiles) of sub-samples with a Hosmer-Lemeshow Chi-squared test.[13,244,245] To perform this, each sample was split into five groups (quintiles) of equal size by sorting each sample by predicted risk in descending order so that the first 20% of patients represented the group with the lowest CVD risk. Then, predicted mean risk was compared to observed mean risk in each quintile. Insignificant Chi-squared test results ($P \geq 0.05$) indicated no differences between observed and predicted mean risks and hence satisfactory calibration of the model.

To further assess the accuracy of the model, the Brier score (mean squared error with score range 0–1) was calculated for both samples. The lower the value of the Brier score, the better the accuracy of the model.[102,246] In addition, sensitivity, specificity, likelihood ratios and positive and negative predictive values were calculated using the derivation sample for cut-off CVD risk values of 5%, 10% and 15% in order to determine the optimal cut-off point for clinical application.[247,248] In addition, the optimal statistical cut-off value of CVD risk was identified as the point where the sum of sensitivity and specificity values yielded the largest value.

3.10 Rigours of the study

The scientific rigour and trustworthiness of a study is usually demonstrated by the reliability and validity of its research processes and measurements.[249] In general, validity refers to how accurate the measurements are and whether the study truly measures that which it aims to measure. Reliability, on the other hand, refers to the consistency of the results of these measurements if they are subsequently repeated or reproduced on different occasions.[249,250]

In this project, the reliability and validity of measurements, especially the laboratory measurements, were ensured through regular periodic checks and calibration of the laboratory equipment and machines using standardised specimens. Furthermore, so as to ensure consistency, the same assay methods for various measurements were used in all laboratories. In addition, all tests were performed by qualified trained laboratory technicians. For the key variables in this study, such as CHD, PAD, stroke and key risk factors, the researcher ensured that the diagnoses were confirmed as per standard procedures and were cross-checked from different sources for data. Measurements for BMI and blood pressure (BP) were conducted by trained nurses using standard calibrated equipment; additionally, more than one BP reading was taken to ensure the reliability of the measurement. Finally, all data collectors were trained and supervised so that the data collection would be carried out consistently and to obtain high-quality data.

3.11 Ethical considerations

Since this study involved a review of clinical patient records with minimal or no direct contact with the participants, any physical and psychological harm to the patients was expected to be very limited. In addition, the following procedures were undertaken to address potential ethical issues:

- Ethical approval was obtained from Griffith University (PBH/01/15/HREC) and the Ministry of Health in Oman before the fieldwork began (see appendix C).
- Permission was obtained from the administration of all involved health institutions to undertake the necessary data collection.
- Written consent from participants was not required as this study used secondary data (the existing health records of diabetic patients) collected by selected institutions. However, in some cases of deficient or missing information, telephone interviews were conducted with the patients. In these circumstances, verbal consent was obtained from the patients prior to the interviews.
- Anonymity of the data was ensured. All patient names and contact details were removed from the data set and a non-identifiable code was given to each individual patient so as to keep his/her records anonymous.
- Confidentiality and privacy of the patients' data was ensured by removing identifying information and links to their personal details. Most importantly, all paper-based and electronic records were stored in locked cabinets and secured computerised files which could only be accessed by the principal researcher.

3.12 Project management

The researcher was responsible for monitoring all research activities. He conducted periodic visits to all fieldwork sites throughout the duration of the project to ensure the quality of data, resolve emerging issues and ensure the progress of various data collection activities in a timely manner. Also, all research activities were overseen by an academic principal supervisor in

order to minimise any potential errors and ethical issues in the conduct of this project.

Summary

This Chapter provided details of the study design, data collection and analysis methods that were used in the execution of this research project. A retrospective cohort study design was applied to two samples of Omanis with type 2 diabetes in Aldakhiliyah Province. In both samples, data on baseline risk factors in 2009–2010 were retrieved from existing records (secondary data) and the patients were tracked from baseline until their first CVD events, their deaths or the end of the follow-up period in December 2015. The following three chapters present the findings in response to the research questions of this research project. Chapter 4 presents the first sub-study in which a cohort of 2,039 patients was used to determine CVD incidence and patterns of CVD risk factors among the target population. It is presented as a published paper in compliance with the required format of a peer-reviewed journal. The same sample was used subsequently in the second sub-study to derive a CVD risk assessment equation for the targeted diabetic population, as presented in Chapter 5. The third sub-study then used a second sample of 405 patients to validate the developed model, as presented in Chapter 6.

Chapter 4: (Paper 2) CVD Incidence and the Patterns of Associated Risk Factors among Omanis with Type 2 Diabetes

4.1 Introduction

The last chapter has addressed the detailed methodologies of this retrospective cohort study which involved the analysis of secondary data. This chapter is presented in the form of a published paper touching on the first research question. Firstly, this chapter presents the incidence of CVD, risk factor prevalence and the crude association patterns between CVD and key risk factors in the Omani type 2 diabetic population. Secondly, the results presented in this chapter forms the base towards developing the required CVD risk assessment model for this specific population, which will be elaborated in chapter 5.

This chapter is presented as a co-authored published original article following the required format/ style of Oman Medical Journal. However, the pages, figures and tables were re-numbered to be consistent with the flow of the thesis. The bibliographic details of the co-authored paper, including all authors, are:

Chapter 4: Al Rawahi AH, Lee P, Al Anqoudi ZAM, Al Busaidi A, Al Rabaani M, Al Mahrouqi F, et al. Cardiovascular Disease Incidence and Risk Factor Patterns among Omanis with Type 2 Diabetes: A Retrospective Cohort Study. Oman Med J. 2017;32(2):106–14. DOI: 10.5001/omj.2017.20.

The chapter commenced with a declaration of authorship followed by an abstract of the published article. Then, it presents the details of the study including the used methods, detailed results, a discussion and a conclusion. It ends with a list of references related to the published article.

Declaration

I am (the candidate) the first and the corresponding author of this paper. My contribution to the paper involved: conception of the research idea, reviewing the literature, designing the research methods, supervising the data collection and data entry, analyzing and interpreting the data, drafting and reviewing the manuscript and publishing it. This contribution is acknowledged by all co-authors.

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Cardiovascular Disease Incidence and Risk Factor Patterns among Omanis with Type 2 Diabetes: A Retrospective Cohort Study

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4.2 Abstract

Objectives: Cardiovascular disease (CVD) represents the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus (T2DM). Its incidence and risk factor patterns vary widely across different diabetic populations. This study aims to assess the incidence and risk factor patterns of CVD events among Omanis with T2DM.

Methods: A sample of 2,039 patients with T2DM from a primary care setting, who were free of CVD at baseline (2009−2010) were involved in a retrospective cohort study. Socio-demographic data and traditional risk factor assessments at the baseline were retrieved from medical records, after which the first CVD outcomes (coronary heart disease, stroke, and peripheral arterial disease) were traced from the baseline to December 2015, with a median follow-up period of 5.6 years.

Results: The overall cumulative incidence of CVD was 9.4% with an incidence density of 17.6 per 1000 person-years. Prevalence of poor glycemic control, hypertension, obesity, dyslipidemia, albuminuria and current smoking were 40.0%, 56.3%, 39.0%, 77.3%, 18.7%, and 7.8%, respectively. The univariate survival analysis showed a significant association between CVD and the following factors: age, diabetes duration, body mass index, glycemic control, hypertension, total serum cholesterol, and albuminuria.

Conclusions: This study revealed a high incidence of CVD and a high prevalence of its traditional risk factors among Omanis with T2DM. In addition, compared to global studies, important differences in the prevalence of some risk factors and their patterns in the univariate association with the cardiovascular outcome have been observed.

Keywords: Incidence; Risk Factors; Cardiovascular Disease; Coronary Heart Disease; Stroke; Type 2 Diabetes; Oman.

Introduction

Coronary heart disease (CHD), stroke, and peripheral arterial disease (PAD) are the main cardiovascular diseases (CVD) among populations with type 2 diabetes mellitus (T2DM).[1–3] CVD incidence varies considerably across diabetic populations. Cumulative incidence of CVD events data from New Zealand and Australia showed that 17.9% and 14.9% of T2DM patients respectively, developed their first CVD event within a five-year mean period of follow-up.[4,5] However, data from China showed much lower rate (4.9%) within a similar follow-up period.[6] Another population-based study showed the seven-year incidence of CHD among patients with diabetes to be around 20% in Finland.[7]

Various traditional risk factors such as male sex, age, obesity, dyslipidemia, hypertension (HTN), poor glycemic control (high glycosylated hemoglobin (HbA_{1c}), albuminuria, smoking, and family history of CVD have been identified to be independent contributors for CVD.[8,9] In addition, other non-traditional factors such as social deprivation and erectile dysfunction as well as other hematological factors were studied later and showed significant association with CVD.[8,9] However, until now there is no sufficient evidence that monitoring of the non-traditional factors leads to better diagnostic and treatment results.[8,10]

In Oman, the prevalence of T2DM reached 12.3% in 2008.[11] Very limited literatures are available relating to CVD occurrence and its risk factors among patients with T2DM in this country. A descriptive study indicated that 54.1% of Omani patients presented for coronary artery bypass surgery were found to be diabetics.[12] Another study among Omani patients with T2DM revealed a high prevalence of CVD risk factors (52.2% were hypertensive, 56.7% with uncontrolled glycemia, and 44.1% with hypercholesterolemia) among the study sample.[13] Consistent results have been observed in the national health survey in 2008.[11] Moreover, other data showed that 42.5% of Omani patients with diabetes were having micro- or macro-albuminuria.[14] However, literature review revealed that no CVD incidence studies nor analytic studies

addressing CVD risk factors have been conducted among Omanis with T2DM.[15]

This study aimed to assess the incidence of CVD events (CHD, stroke, or PAD), the patterns of CVD traditional risk factors, and conduct preliminary survival analysis of the traditional risk factors of CVD among Omanis with T2DM in Al Dakhiliyah Governorate (Province) of Oman. This study is a part of a project that involves patients with T2DM residing in Al Dakhiliyah Governorate. It has been established to study the CVD risk, its risk factors, and ultimately, develop a risk prediction tool that is suitable to estimate the five-year CVD risk among T2DM patients in Oman.

4.3 Methods

This study employed a retrospective cohort design. The reference population was Omani patients with T2DM residing in Al Dakhiliyah Governorate in which diabetes care is delivered through the National Diabetes Control Program in 25 primary care institutions consisting of four polyclinics and 21 health centers. As per the diabetes control program guidelines, diabetes mellitus (DM) diagnosis is done based on the World Health Organization (WHO) cut off points. All patients were assessed at DM diagnosis, and then assessed at least annually for main risk factors and diabetes complications including CVD, using standardized assessment forms and following standardized diabetes follow-up procedures.[16] All patient assessments in these institutions are administered by diabetologists, trained general physicians, and, trained nursing staff. The laboratory tests were conducted by qualified laboratory technicians. All patients' data were computerized and maintained in the diabetes registry system. Out of the 25 institutions, three polyclinics (Nizwa, Bahla, and Izki Polyclinics) and one large health center (Manah Health Centre) were selected for this study and the year 2009−2010 was considered as the baseline.

The sampling frame included all Omanis with T2DM who were recorded in the diabetes registry of the four selected institutions, who were free of CVD at baseline and showed regular follow-up visits. The patients were followed-up

until the CVD outcome occurred, died, or reached end of data collection in December 2015. Exclusion criteria included patients with no annual assessment on the key factors at baseline, patients with no CVD outcome assessment at baseline, and those who developed non-ischemic heart diseases or limb amputations of non-ischemic causes in the follow-up period. In addition, patients with end stage kidney disease and liver cirrhosis were also excluded. After applying the inclusion/exclusion criteria, eligible patients for the study reached 2039.

Demographic data, data related to risk factors at baseline, and CVD outcome data were gathered by trained staff using a well-designed data collection sheet. The data was retrieved from the patients' medical records of the selected institutions. Sex, age at baseline, age at T2DM diagnosis, diabetes duration, body mass index (BMI), HbA_{1c}, HTN, blood pressure (BP) control, lipid entities, albuminuria, smoking, and first degree family history of CVD were the baseline factors considered in this study.

The CVD outcome was defined as the first fatal or non-fatal CHD event, stroke, or PAD event, diagnosed by specialized physicians based on the clinical assessment and confirmed using diagnostic tests. CHD diagnosis included stable angina, unstable angina, and myocardial infarction, and was confirmed by 12-lead electrocardiograms (ECG) and a serum troponin test. However, ECG stress test (Treadmill test) and coronary angiography were needed in instances where diagnosis was not clear. In addition, stroke was confirmed by computed tomography (CT) scan while PAD was confirmed by either clinical diagnosis of gangrene, limb amputation due to an ischemic cause, or a clinical picture of an ischemic limb confirmed by ankle-brachial index pressure and angiography. The same diagnostic criteria were applied at the baseline to ensure that the included participants were free from CVD at the beginning of the study.

The CVD outcome was traced from baseline to December 2015 (maximum of seven-year follow up) using the same data sources by reviewing physician's clinical notes and diagnosis for each patients and for all visits in the follow-up period. Causes of death were retrieved from death certificates. Definitions of

CVD outcome and main risk factors are shown in Table 4.1. Cut off points of various factors are considered as per the national diabetes management guideline manual.[16]

To ensure the quality of the data, different resources of data like patients' soft files and diabetes registers were cross-checked. Causes of death were cross-checked from patient's soft files where applicable. In addition, around 10.0% of the collected data was re-checked for consistency.

Data was analyzed using SPSS Statistics (SPSS Statistics Inc., Chicago, US) version 20.0 . Incidence was expressed in percentage with 95% confidence intervals (CI). Categorical variables were presented in numbers and percentages while continuous variables were described as mean with standard deviation (SD). Continuous variables were then categorized into different levels according to clinical definitions. The univariate relationship between the CVD risk and each of the key risk factors was assessed using Kaplan-Meier (KM) survival analysis (with log-rank, Breslow and Tarone-Ware test), and chi-squared test including odds ratios (OR) and 95% CI. In addition, Analysis of variance (ANOVA) test was used to assess the crude relationship between continuous and categorical variables when required. A p-value ≤ 0.050 was considered statistically significant.

This study was approved by the Regional Research and Research Ethics Committee of the Ministry of Health in Oman, and Griffith University Research Ethics Committee as well. Due to the retrospective nature of this study, informed consent was not required and permission from involved institutions was obtained to start data collection. However, in some instances phone calls along with verbal consent were required to confirm smoking status and family history of CVD.

Table 4.1: Definitions of the cardiovascular outcome and the main risk factors.

Variables	Definition and cut-off points
CVD outcome	Time to the first fatal or non-fatal CVD recorded events from the following list: - Confirmed physician diagnosis of CHD in form of: stable angina, unstable angina, or acute myocardial infarction. - Confirmed physician diagnosis of ischemic or hemorrhagic stroke. - Confirmed physician diagnosis of PAD (ischemic limb, gangrene, or amputation).
HTN	Physician diagnosis of HTN (SBP ≥ 140 mmHg or DBP ≥ 90 mmHg confirmed in BP chart readings after excluding other causes)
Uncontrolled BP	SPB ≥ 140 mmHg or DBP ≥ 90 mmHg
High risk total cholesterol	Total cholesterol ≥ 5.2 mmol/L
High risk LDL	LDL ≥ 2.6 mmol/L
High risk HDL	HDL ≤ 0.9 mmol/L for males and ≤ 1.3 for females
High risk TG	TG ≥ 1.7 mmol/L
Dyslipidemia	At least one of the following: high risk cholesterol; high risk LDL; high risk HDL or high risk TG.
Albuminuria (micro or macro)	Persistent albumin/creatinine ratio of ≥ 2.5 in males and ≥ 3.5 in females, confirmed at least twice within three months or more after excluding other possible causes.
Glycemic control	Good glycemic control is considered if HbA_{1c} of < 7%, borderline control if HbA_{1c} 7−8% and poor control if > 8%
Obesity BMI	BMI = body weight / square of height in meters. Overweight was defined as BMI ≥ 25, obese as BMI ≥ 30, and morbid obesity as BMI ≥ 35

CVD: cardiovascular disease; CHD: coronary heart disease; PAD: peripheral arterial disease; HTN: hypertension; SPB: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; HbA_{1c}: glycosylated hemoglobin; BMI: body mass index.

4.4 Results

Out of the total sample of 2,039, 64.0% were female. The mean age at baseline was 54.5±11.4 years, with minimum and maximum ages of 22.9 and 95.8 years, respectively. The mean age at diabetes mellitus (DM) diagnosis was 48.3±11.0, with minimum and maximum of 20 and 91 years, respectively. Contributions of the number of patients taken from the four selected institutions (Nizwa, Bahla, Izki, and Manah) in the total sample were 42.3%, 30.7%, 15.0% and 12.0%, respectively, which were matched with the patient distribution covered by each institution. The mean, median, and maximum years of follow up were 5.3±1.1, 5.6, and 7.0, respectively. The study involved 10910 person-years among the study sample. The mean DM duration at baseline was 5.8±4.1 years with 47.0% and 21.0% of the study sample had DM duration of < 5 and > 10 years, respectively. Further details on the baseline characteristics of the study sample are shown in Table 4.2.

The total cumulative incidence of CVD in this study was 9.4% (= 192/2039; 95% CI: 8.1% - 10.7%) over the study period with 9.8% and 9.2% among males and females respectively (no significant difference, p = 0.45). The incidence density was 17.6 per 1000 person-year. Of the 192 CVD events, CHD, stroke and PAD constituted 72.4%, 20.3% and 7.3% respectively. Fatal CVD events were observed in 7.3% of the total CVD events. The highest annual incidence rate of CVD was 2.1% in the year 2014, the lowest was 0.7% in 2010, and the average was 1.6% per year.

Cumulative incidence has varied significantly ($p < 0.001$) across institutions with the highest (17.6%) in Izki polyclinic and the lowest in Bahla polyclinic (6.1%). With regard to sample size, > 70.0% of the total sample was taken from Nizwa and Bahla polyclinics, since they cover much larger catchment area compared to other institutions. Mean follow-up periods in different institutions varied between 5.0 and 5.4 years, being longest in Nizwa and lowest in Izki. Poor glycemic control in Izki, Manah, Nizwa, and Bahla was observed in 46.2%, 41.0%, 36.0%, and 41.0%, respectively, while the mean diabetes duration in different institutions varied between 5.5 years and 6.0 years.

Table 4.2: Baseline characteristics of the study sample and *p* values of crude association of various factors with CVD

Characteristic	Mean ±SD	Groups	Percentage % (n/N)	Crude OR (95% CI)	Chi-square *p* value
Total number	**2039**				
Sex		Male	36 (734/2039)	1.1 (0.8 – 1.5)	0.45
Age at baseline, years	54.5 ± 11.4	<40 yrs.	10.9 (223/2039)	1	< 0.001
		40 - 60	56.9 (1161/2039)	4.8 (1.7 – 13.1)	
		≥ 60	32.1 (655/2039)	9.3 (3.4 – 25.6)	
Age at DM diagnosis, years	48.3 ± 11.0	<40 yrs.	21.3 (434/2039)	1	< 0.001
		40 - 50	33.2 (677/2039)	3.3 (1.7 – 6.2)	
		≥ 50	45 (928/2039)	5.3 (2.9 – 9.7)	
DM duration, years	5.8 ± 4.1	< 5 yrs.	47.2 (962/20139)	1	< 0.001
		10 –15	31.8 (649/2039)	2.6 (1.8 – 3.7)	
		≥ 10	21 (428/2039)	2.5 (1.7 – 3.8)	
BMI, kg/m^2	29.2 ± 5.4	< 25	22.1 (426/1929)	2.4 (1.3 – 4.3)	0.01
		25 - 30	38.9 (751/1929)	1.9 (1.1 – 3.4)	
		30 - 35	25.2 (486/1929)	1.4 (0.7 – 2.5)	
		≥ 35	13.8 (266/1929)	1	
HbA_{1c}, %	7.9 ± 2.2	< 7	41.1 (777/1891)	1	0.01

		7 – 8	19.1 (362/1891)	1.0 (0.6 – 1.6)	
		≥ 8	39.8 (752/1891)	1.6 (1.1 – 2.2)	
HTN		Present	56.3 (1148/2039)	2.1 (1.5 – 2.9)	< 0.001
SBP, mmHg	129.3 ± 14.1	≥ 140	28.2 (561/1989)	1.1 (0.8 – 1.6)	0.45
DBP, mmHg	78.8 ± 7.4	≥ 90	15.1 (301/1989)	1.2 (0.8 – 1.7)	0.47
Total cholesterol, mmol/L	5.0 ± 1.1	≥ 5.2	37.8 (765/2023)	1.4 (1.0 – 1.9)	0.03
LDL, mmol/L	3.2 ± 1.0	≥ 2.6	71.7 (1015/1415)	1.3 (0.8 – 1.9)	0.30
HDL, mmol/L	1.2 ± 0.4	≤ 0.9	57.9 (844/1458)	1.2 (0.8 – 1.8)	0.31
TG, mmol/L	1.72 ± 1.1	≥ 1.7	38.1 (768/2018)	1.0 (0.7 – 1.3)	0.75
Dyslipidemia		Present	77.3 (1569/2030)	1.0 (0.8 – 1.4)	0.80
Albuminuria		Present	18.7 (269/1441)	3.4 (2.4 – 5.0)	< 0.001
Family history of CVD		Present	21.4 (316/1480)	1.3 (0.8 – 2.0)	0.25
Smoking		Current	7.8 (82/1056)	1.4 (0.6 – 1.4)	0.45

SD: standard deviation; CI: confidence interval; OR: odds ratio; DM: diabetes mellitus; CVD: cardiovascular disease; HTN: hypertension; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL: low density lipoprotein; HDL: high density lipoprotein; TG: triglycerides; HbA_{1c}: glycosylated hemoglobin; BMI: body mass index.

Baseline data among the study group showed a high prevalence of the CVD traditional risk factors [Table 4.2]. The mean BMI was 29.2±5.4 kg/m^2 , and 38.9% were overweight (BMI 25–30) and similar proportion were obese (BMI ≥ 30). Poor glycemic control was also a dominating risk factor. The mean

HbA_{1c} was 7.9±2.2%, and around 40.0% and 19.0% of the study sample were having poor (HbA_{1c} > 8%) and borderline (HbA_{1c} 7–8%) glycemic control at baseline, respectively. Dyslipidemia was observed in about 77.0% of the study sample. The mean cholesterol level was 5±1.1 and 37.8% of the participants had total cholesterol level of ≥ 5.2 mmo/L. In addition, 71.7%, 58.0%, and 38.1% of the study sample had high risk low density lipoprotein (LDL), high risk high density lipoprotein (HDL), and high risk triglycerides (TG), respectively. The mean systolic blood pressure (SBP) was 129.3±14.1 and 56.3% of the participants were hypertensive, of which 46.6% had uncontrolled BP. Moreover, micro/macro-albuminuria, first degree family history of CVD, and smoking were observed in 18.7%, 21.4%, and 7.8%, respectively.

The crude survival analysis using KM survival curves along with the ORs and chi-square test showed significant association between CVD risk and the following factors: age, HbA_{1c}, albuminuria, BMI, DM duration, HTN, and total cholesterol. Table 4.2 presents the distributions of different factors in the study sample and their crude associations with CVD outcome.

Age at baseline was observed to have the strongest association with CVD among all predictors. Figure 4.1 shows a sharp increase in the CVD risk over time with increasing age. The crude OR for patients aged ≥ 60 years compared to patients aged < 40 years was 9.3 (95% CI 3.4–25.6, $p < 0.001$). Similarly, the increase in the hazard trend of CVD risk over time was sharper among patients with DM duration 5–10 years and ≥ 10 years compared to those with DM duration < five years (crude OR for both groups is 2.5, 95% CI 1.7–3.8, $p < 0.001$). However, there was no difference in the hazard trend of CVD risk between the two former groups ($p = 0.800$). The difference in hazard trend of CVD risk between the good glycemic control and the poor glycemic control groups was also observed to be significant (OR 1.7, 95% CI 1.1–2.2). However, there was no significant difference in hazard trend between good and borderline glycemic control groups ($P = 0.900$).

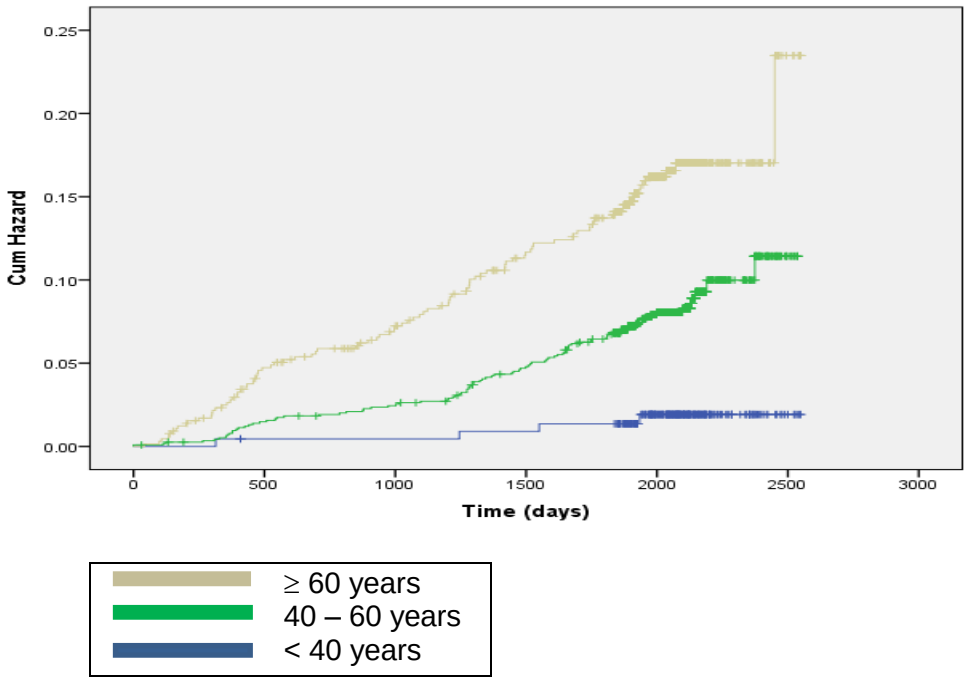

Figure 4.1: Cardiovascular disease hazard function according to the age groups at baseline

BMI was observed to be inversely related to the CVD risk [Figure 4.2]. The ORs showed increasing trend with decreasing BMI levels. The highest group at risk was the group with the normal BMI compared to the lowest one, which was the one with morbid obesity (OR 2.4, 95% CI: 1.3–4.3). However, ANOVA test showed that the mean DM duration was significantly higher among normal weight patients (2,220 days) compared to the obese patients (2,010 days), with *p*-value = 0.047. Moreover, HTN, albuminuria, and high total cholesterol were also observed to be strongly associated with increasing hazard trends of CVD risk (crude ORs and 95% CI: 2.1, 1.5– 2.9; 3.4, 2.4–5.0; and 1.4, 1.01–1.9, respectively).

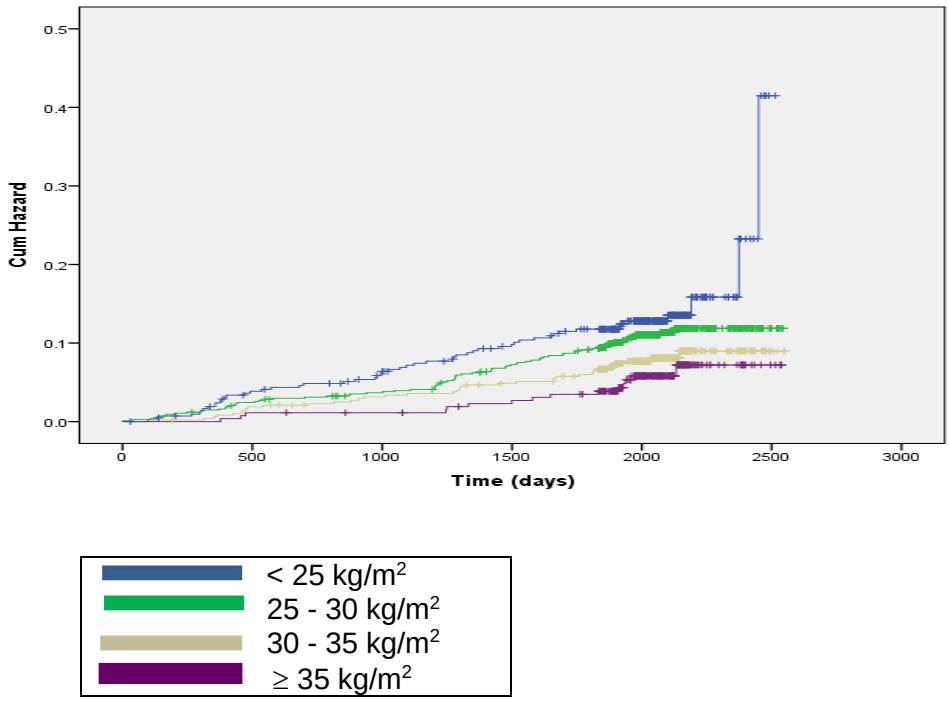

Figure 4.2: Cardiovascular disease hazard function according to body mass index groups

4.5 Discussion

Findings of this longitudinal study included the high five-year CVD cumulative incidence (9.4%); the high prevalence of main CVD risk factors like HTN, obesity, poor glycemic control, dyslipidemia, and albuminuria; and the insignificant association between CVD and some of the traditional risk factors such as smoking and family history of CVD in the crude analysis.

CVD incidence varies considerably across different populations with diabetes, depending on the study setting, ethnic background, inclusion criteria, CVD outcome definition, and duration of the follow-up. Unfortunately, no longitudinal studies could be found in the literature related to CVD incidence among T2DM patients in the neighboring Arabian countries. However, globally, some studies showed a lower incidence compared to ours, while others showed a much higher incidence. Studies in general practice settings in Scotland and China showed that 5.3% and 4.9% of T2DM developed CVD within median periods of 4.1 and 5.4 years, respectively.[6,17] However, in these two studies the considered outcome was CHD alone. An Italian population

based study revealed a cumulative incidence of 7.6%.[18] However, the study had a short follow-up period (four years) and the outcome included only CHD. In contrast, many other studies demonstrated much higher incidence. In this context, the Finnish and the ARIC population based studies in Finland and U.S found that the cumulative incidence of CHD alone to be 20.2% and 17.1% over periods of seven and 10 years, respectively.[7,19] Alternatively, in England, the CVD incidence was observed to be 17.9% over a period of 5.5 years.[20] In the Finnish and ARIC studies, patients less than 45 years of age were not included and they involved a relatively longer periods of follow-up. Whereas the possible reason for the higher CVD incidence in the English study was that the CVD outcome included other cardiovascular abnormalities like heart failure and arrhythmias in addition to CHD, PAD, and stroke. Longitudinal data from community based and primary care settings in Australia and New Zealand showed higher four-year and five-year CVD events cumulative incidence (14.9% and 17.9%, respectively) compared to the present study.[4,5] While sudden death was not included in the CVD outcome in the present study, it was included in the Australian study. The New Zealand study involved a longer duration of follow-up (eight years). Thus, our relatively lower incidence maybe explained partially by the non-selective sampling since the participants age ranged between 22.9 and 95.8 years, intermediate period of follow-up (mean of 5.3 years), and that the definition of CVD was confined to CHD, PAD, and stroke, excluding sudden death. However, the expected variation in the CVD incidence in populations with different ethnicities, lifestyles and cultures might be a better explanation.[15]

In this study, CVD incidence varied considerably across the involved four institutions. It was higher among Izki polyclinic and Manah health center compared to Nizwa and Bahla polyclinics. This may be explained by the higher prevalence of poor glycemic control in Izki and Manah. In addition, since more than 70% of the total sample was taken from Nizwa and Bahla polyclinics, this might had an effect on the observed difference.

The present study showed a high prevalence of most of the traditional risk factors such as obesity, poor glycemic control, HTN, dyslipidemia, and

albuminuria. Some of the traditional factors have been excluded in the univariate association with CVD risk. Many of previous longitudinal studies with similar cohorts have shown similar results, however, some important differences were observed.[4,17,20,21] For example, current smoking in the present study showed a low prevalence (7.8%) and was not associated with CVD. A longitudinal study among English patients with diabetes showed the prevalence of current smoking to be around 34% in men and 25% in women, while in New Zealand it was 15%.[4,21] Other global studies even with low CVD incidence have also showed higher prevalence of smoking among the study groups.[6,10,17] Although most of the related studies showed significant association between smoking and CVD, some of them have revealed insignificant association even in the univariate analysis.[5,10,18] Low prevalence of smoking among general population and population with diabetes in Oman has been observed by many studies.[22–24] This may be explained by the social and cultural stigma towards this habit, which may prevent people from smoking or may result in under-reporting. These are the potential reasons for the insignificant association between smoking and CVD observed in this study.

Although the observed high proportion of obesity is consistent with many previous local and global studies,[4,11,17,20,21] the inverse univariate association with CVD is another interesting finding conflicting with many related studies.[5,18,19] However, other studies revealed an insignificant role for obesity in CVD occurrence.[25,26] Therefore, a sort of controversy in the independent role of obesity in CVD occurrence among populations with diabetes is still there.[8] In the present study, this relationship maybe confounded by the diabetes duration which was significantly higher among obese patients as shown by the ANOVA test. However, future studies can assess this in more details.

High levels of total cholesterol, LDL and TG, and low levels of HDL were observed to be of high prevalence in this study and in many other local and global studies.[10,13,17] However, the insignificant univariate association between CVD and lipid entities (LDL, HDL, and TG) except the total cholesterol, is

another interesting finding related to the pattern of CVD risk factors. LDL, HDL, and/or TG have shown significant association with CVD in many studies,[5,19,27] however, serum cholesterol was also observed to be associated with CVD in the univariate and/or multivariate analysis.[17–19,21] However, the insignificant association between CVD and other lipid entities was also observed in other studies.[10,17] Since different good quality studies can yield different association results, not only for the lipid factors, but for other factors as well, it seems that the pattern of CVD associations with different factors is affected by population characteristics. It is likely that different populations may yield different results.

Despite the well-known relationship of CVD with gender and first degree family history of CVD revealed by many studies,[4,5,10,17,28] our study showed insignificant associations. However, the same was observed in some studies for the latter,[6,18] which may be explained by the recall bias in reporting this risk factor.

This study was the first longitudinal study addressing the CVD incidence and risk factor patterns among T2DM patients in Oman and the neighborhood Arab countries. In addition, it involved a good sample size taken from primary care settings where all diabetic patients are registered and managed, and hence the sample is likely to be a representative one. In contrast, the problems of recall bias and missing data were major constraints due to the retrospective nature of the study. However, these were partially overcome by cross-checking different sources of data. In addition, types of anti-diabetes, anti-hypertensive, and anti-lipid drugs were not included in this study. However, the effects of anti-diabetes, anti-hypertensive, and anti-lipid treatments are expected to be included in the levels of diabetes control, HTN control, and lipid profile to some extent, respectively. Similarly, physical inactivity was not considered in this study due to the difficulties in quantifying and gathering the related data.

4.6 Conclusion

The incidence of CVD and the prevalence of its risk factors among Omanis with T2DM were both high. In addition, important differences in the picture of the CVD risk factors and their preliminary associations with CVD compared with global studies have been observed. This may be attributed to the strong relationship between the geographical location of the patients' environmental and lifestyle factors with diabetes complications.[15,29]

Disclosure

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Chapter 5: (Paper 3) Cardiovascular Risk Prediction Model for Omanis with Type 2 Diabetes

5.1 Introduction

The last chapter addressed the first research question regarding the incidence of CVD and patterns of CVD risk factors among Omani type 2 diabetics. It also provided preliminary crude associations between CVD incidence and key risk factors in this population. This chapter is a continuation of the previous work developing the required CVD risk assessment tool. In this chapter, the second research question relating to developing a suitable CVD risk prediction model for this population is addressed. Further assessments on the independent risk factors for CVD are presented, using adjusted survival analysis methods. In addition, the baseline survival function is obtained in order to model the CVD risk tool for this specific population in the form of a statistical equation.

This chapter is presented as a co-authored original article following the formatting/style requirements of *'Primary Care Diabetes'* journal. However, the pages, figures and tables are re-numbered to be consistent with the flow of the thesis. The bibliographic details of the co-authored paper, including all of the authors, are

Al Rawahi AH, Lee P, Al-Anqoudi ZAM, Alrabaani M, Al-Busaidi A, Almahrouqi F, Al-Busaidi AM. Cardiovascular Risk Prediction Model for Omanis with Type 2 Diabetes. Manuscript submitted for publication to *'Primary Care Diabetes'* journal. 2017.

This chapter starts with a declaration of authorship followed by an abstract of the article. Subsequently, it presents the details of the study, including the methods used, detailed results, a discussion and a conclusion. A list of references related to the article is given at the end of this chapter.

Declaration

I am (the candidate) the first and the corresponding author of this paper. My contribution to the paper involved: conception of the research idea, reviewing the literature, designing the research methods, supervising data collection and entry, and writing and revising the manuscript. This contribution is acknowledged by all co-authors.

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Cardiovascular Risk Prediction Model for Omanis with Type 2 Diabetes

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5.2 Abstract

Introduction

To date, no cardiovascular risk assessment tool has been developed specifically for any Arabian population including Omanis. This study aims to develop a suitable cardiovascular risk prediction model in the form of a statistical equation, for Omanis with type 2 diabetes.

Methods

A sample of 2039 patients with type 2 diabetes selected from primary care settings in the Aldakhiliyah Province of Oman were involved in a retrospective cohort study. All patients were free of cardiovascular disease at baseline (in 2009-2010) and were followed up until: 1) their first cardiovascular event occurred; 2) the patient died, or 3) the end of the data collection in December 2015.

Results

Among the total sample, 192 cardiovascular disease events were recorded within a mean follow-up period of 5.3-year. The 5-year probability of a cardiovascular event was given as $1 - 0.9991^{Exp\sum XiBi}$, where $Exp \sum XiBi$ (hazard ratio) = *Exp* (0.038 age + 0.052 DM duration + 0.102 HbA1c + 0.201 total cholesterol + 0.912 albuminuria [1 if present] + 0.166 hypertension [1 if present] + 0.005 BMI).

Conclusion

The first cardiovascular risk prediction tool in the Arab world was developed in this study. It may be used to estimate the 5-year cardiovascular risk among Omanis with type 2 diabetes in order to plan patient management and preventive measures. However, further validation studies are required to determine the accuracy of the model.

Key words: Cardiovascular disease; Risk prediction; Model; Type 2 diabetes; Arab; Oman

Highlights

- This paper presents the first cardiovascular risk prediction tool in the Arab world.
- It includes seven traditional CVD predictors to calculate the 5-year CVD risk for Omani diabetic patients.
- Predictors included in the model are: age, diabetes duration, glycosylated haemoglobin, albuminuria and cholesterol, body mass index and hypertension

Introduction

Cardiovascular disease (CVD) in the form of coronary heart disease (CHD), stroke and peripheral arterial disease (PAD) represents the leading cause of morbidity and mortality among patients with type 2 diabetes mellitus (DM) [1]. Diabetics are thought to have a two-to-four-fold increase in the risk of developing CHD compared to non-diabetics [2]. In addition, it is estimated that 50% of diabetic patients die prematurely of a cardiovascular cause [1].

Various professional guidelines for the management of type 2 diabetes have advocated the use of CVD risk assessment tools to estimate CVD risk in type 2 diabetics using traditional CVD predictors such as hypertension (HTN), dyslipidemia, high glycosylated hemoglobin (HbA1c), albuminuria, obesity, smoking, and family history of CVD [3,4]. CVD risk estimation is important to plan for the initiation of preventive and therapeutic measures including anti-lipid, anti-hypertensive and anti-platelet therapies, as well as appropriate health education [3,4]. Some examples of such tools which are usually presented as statistical equations or risk charts include: the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) study model; the Australian Fremantle Diabetes Study model; the Chinese Total CHD Risk Score; the U.S. Atherosclerosis Risk in Communities (ARIC) model; the U.K. Prospective Diabetes Study (UKPDS) risk engine for

diabetes patients, and the World Health Organization (WHO)/International Society of Hypertension (ISH) risk prediction charts [5-10].

In Oman, as in other Arabian countries, type 2 diabetes has become a great public health burden [11,12]. However; very limited literature is available related to CVD occurrence and its risk factors among type 2 diabetics in this region. In addition, most of the available data are descriptive in nature. As such, a previous study found that 54.1% of Omani patients presenting for coronary artery bypass surgery were diabetic [13], and local statistical reports have shown that more than 50% of amputations in Oman were due to DM [14]. In addition, a high prevalence of common CVD risk factors was observed among Omani diabetics [12].

With regards to CVD risk assessment tools, no CVD risk assessment model has yet been developed for any of the Arabian populations including Omanis. Despite the availability of the international risk assessment tools, they are not considered optimal for Omani and Arabian diabetics. This is mainly due to the differences in lifestyle patterns, socio-demographic characteristics and patterns of CVD risk factors in these populations, as addressed in a recent review [15].

To fill this gap, the present study aims to develop a risk assessment tool in the form of a statistical equation suitable for estimating the 5-year CVD risk among Omanis with type 2 diabetes.

5.3 Methods

Study design and subjects

This retrospective cohort study was conducted between September, 2015 and July, 2016. Omanis with type 2 diabetes residing in the Aldakhiliyah Governorate (Province) of Oman were considered to be the reference population. Diabetes care services in this region are delivered through the National Diabetes Control Programme via four polyclinics and 21 health centres. All patients are assessed for the main risk factors and complications of DM at the initial DM diagnosis and are then reassessed at least once a

year. A diabetes diagnosis in these institutions is made according to WHO criteria. Standardised assessment forms and management procedures are implemented following the diabetes care manual [16,17]. In these institutions, patient DM diagnoses, associated health assessments and data recording are performed by diabetologists and trained general physicians, as well as trained nursing staff. All patient-related data are maintained in computerised files and in diabetes registers. Three polyclinics (Nizwa, Bahla and Izki Polyclinics) and one large health centre (Manah Health Centre) were selected as the study institutions. The year 2009–2010 was considered to constitute the baseline.

All Omanis with type 2 diabetes who were recorded in the diabetes registry of the four selected institutions; free of CVD at the baseline; and showed regular followed ups were included in the sampling frame. Exclusions included patients with no annual assessment on the key factors and CVD outcomes at the baseline, and those who developed non-ischemic heart diseases or who underwent limb amputations for non-ischemic causes during the follow-up period. Patients with end-stage kidney disease and liver cirrhosis were also excluded. After applying these inclusion/exclusion criteria, a total of 2,039 patients were eligible and were included in the study. These patients were then followed-up until their first CVD event occurred, they died or until the end of the data collection period in December 2015.

Data collection and definitions

A well-designed data collection sheet was used to collect all related data including demographic data, data related to CVD risk factors at baseline and the CVD outcome. These data were retrieved by trained staff from the diabetes registers and from patient computerised files in the selected institutions. The following baseline factors were considered in this study: gender, age, diabetes duration, body mass index (BMI), HbA1c, HTN, blood pressure (BP) control, total cholesterol level, low density lipoprotein (LDL) level, high density lipoprotein (HDL) level, triglycerides (TG) level, dyslipidemia, albuminuria, smoking status and first-degree family history of CVD.

A CVD outcome was diagnosed by specialized physicians based on the clinical presentation and confirmed using diagnostic tests. A CVD outcome was defined as the first fatal or non-fatal CHD, stroke or PAD event. CHD diagnosis was confirmed by electrocardiograms (ECG) and a serum troponin test. However, in some instances an ECG stress test (Treadmill test) and coronary angiography were required to confirm the diagnosis. In addition, a computed tomography (CT) scan was used to confirm a stroke event, while one of the following criteria was used to diagnose PAD: intermittent claudication confirmed by angiography; clinical diagnosis of gangrene; or limb amputation due to an ischemic cause. To ensure that the included participants were free from CVD at the beginning of the study, the same diagnostic criteria were applied at the baseline.

CVD Outcomes were tracked from baseline until December 2015 (i.e. a maximum follow-up period of 7 years) by reviewing the clinical notes and diagnosis for each patient and for all visits during the follow-up period. In addition, as the CVD outcomes included fatal events, death certificates were checked to confirm the causes of death. Table 5.1 presents the definitions of CVD outcomes and key risk factors.

Data analysis

Data were analysed using SPSS software, Version 22.0. Categorical variables were presented in total counts and percentages while continuous variables were expressed in means and standard deviations (SDs). Chi-squared tests and independent T-tests were used to assess differences between proportions and differences between means respectively, in relation to different risk factors and outcome status. The crude associations between CVD outcome and its predictors were assessed by Kaplan Meier (K.M) survival analysis with log rank, Breslow and Tarone-Ware tests. Cox regression modelling was used to identify independent associated risk factors with CVD and to develop the CVD risk equation. The equation was constructed using all associated CVD factors identified in the crude analysis. A *P* value of ≤ 0.05 was considered statistically significant. Log minus log (log

Table 5.1

Definitions of cardiovascular outcome and main risk factors

Variable	Definition and cut-off points
CVD outcome	The first fata or non-fatal CVD recorded events from the following list: • Confirmed physician diagnosis of CHD in form of: stable angina, unstable angina, or acute myocardial infarction. • Confirmed physician diagnosis of ischemic or haemorrhagic stroke. • Confirmed physician diagnosis of PAD (ischemic limp, gangrene or amputation).
HTN	Physician diagnosis of HTN (systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg confirmed in BP chart readings after excluding other causes).
Uncontrolled blood pressure	SPB ≥ 140 mmHg or DBP ≥ 90 mmHg
Albuminuria (micro or macro)	Persistent albumin/creatinine ratio of ≥ 2.5 in males and ≥ 3.5 in females, confirmed at least twice within three months or more, after excluding other possible causes.
Dyslipidaemia	At least one of the following: Total cholesterol ≥ 5.2 mmol/l; LDL ≥ 2.6 mmol/l; HDL ≤ 0.9 mmol/l for males and ≤ 1.3 for females or TG ≥ 1.7mmol/l.

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; PAD, peripheral arterial disease; HTN, hypertension; SPB, systolic blood pressure; DBP, diastolic blood pressure; LDL, low density lipoprotein; HDL, high density lipoprotein; TG, triglycerides.

– log) plots for categorical predictors of CVD were used to assess the satisfaction of the proportional hazard assumption of the Cox regression method. In addition, model fit was tested by comparing changes in the -2 log likelihood statistic.

Based on the Cox regression results, the t-year CVD probability equation was constructed using the baseline survival probability function *($S_0(t)$)* and expressed as:

t-year CVD probability = 1 - $S_0(t)^{Exp\sum XiBi}$, where $Exp \sum XiBi$ represents the hazard ratio (HR), *Xi* represents the factors included in the model and *Bi* represents the factor coefficients in the model [18,19].

This study was ethically approved by both the Regional Research and Research Ethics Committee of the Ministry of Health in Oman and the Griffith University Research Ethics Committee.

5.4 Results

Out of the total sample of 2,039 patients, 64% were female. Age at baseline ranged from 22.9 to 95.8 years with a mean age ± SD of 54.5 ± 11.4 years, while the mean DM duration was 5.8 ± 4.1 years. The mean ± SD, median and maximum follow-up periods were 5.3 ± 1.1, 5.6 and 7.0 years, respectively. The total person-years of follow-up involved in the study sample was 10,910. Further details of the baseline characteristics of the study sample are illustrated in Table 5.2. Among the total sample, 192 CVD events were recorded during the study period, of which CHD, stroke and PAD constituted 72.4%, 20.3% and 7.3%, respectively.

The following factors were observed to be significantly associated with CVD risk using the univariate survival analysis: age at baseline; age at DM diagnosis; HbA1c; albuminuria; BMI; DM duration; HTN and total cholesterol. All the other factors (gender, BP control, LDL, HDL, TG, dyslipidemia, current smoking and first-degree family history of CVD) were not associated with CVD risk.

Out of the total sample, patients with at least one CVD risk factor missing were excluded for the further multivariate Cox regression analysis. Therefore, a total sample of 1314 patients with complete data was used to construct the final CVD risk equation. Both the included and excluded subjects were similar in the total CVD incidence (9.6% vs. 9.1%). Similarities were also observed in the incidence of each component of CVD (IHD: 72.4% vs. 72.2%; stroke: 20.3% vs. 20.6% and PAD: 7.3% vs. 7.1%). In addition, they were similar with

Table 5.2

Baseline characteristics and cardiovascular outcome among the whole sample and subjects with complete data

Characteristic	Whole sample, % or mean ± SD	Subjects with complete data, % or mean ± SD (n = 1,314)
Sex (female)	64% (1305/2039)	64.1%
Age (years)	54.5 ± 11.4 (for 2039)	55.3 ± 11.0
DM duration (years)	5.8 ± 4.1 (for 2039)	6.6 ± 4.0
Dyslipidemia (present)	77.3% (1569/2030)	77.9%
Total cholesterol (mmol/l)	5.0 ± 1.1 (for 2039)	4.9 ± 1.1
HbA1c % (mmol/mol)	7.9 ± 2.2 (63 ± 17) (for 1891)	7.9 ± 2.2 (63 ± 17)
BMI (kg/m^2)	29.2 ± 5.4 (for 1929)	29.1 ± 5.3
Albuminuria (present)	18.7% (269/1441)	18.6%
HTN (present)	56.3% (1148/2039)	58.6%
Smoking (present)	7.8% (82/1056)	6.8%
1st degree family history of CVD (present)	21.4% (316/1480)	20%
CVD outcome (present)	9.4% (192/2039)	9.6%

Abbreviations: SD, standard deviation; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; BMI, body mass index; HTN, hypertension; CVD, cardiovascular disease.

regards to key variables such as gender (females: 64.1% vs. 63.9%), mean age (53.1 ± 12.1 vs. 55.3 ± 11.0), mean HbA1c (7.9 ± 2.2 vs. 8.0 ± 2.3 in %), mean cholesterol (4.9±1.1 vs. 5.1±1.1), mean BMI (29.1±5.3 vs. 29.3±5.3) and albuminuria prevalence (18.6% vs. 19.8%). However, some differences were observed between the included and excluded subjects. In this regard, HTN was more prevalent among the included subjects (58.6% vs. 52.1%), while first degree family history of CVD was more prevalent among the excluded subjects (25% vs. 20%). The comparisons of participant characteristics at baseline between the two samples are presented in Table 5.2. The included sample was similar to the whole sample not only demographically but also in many key variables. With regard to distribution of participants according to institutions in the whole sample and included sample

respectively, 42% vs. 41% were from Nizwa, 31% vs. 39% from Bahla, 15% vs. 9% from Izki and 12% vs. 11% from Mnah. The distributions also differed minimally.

Risk factors with *P* values ≤ 0.05 in the crude analysis were included in the Cox regression analysis to build the final model. Age at baseline, DM duration, HbA1c, albuminuria and total cholesterol were significantly independent predictors for CVD outcome. Table 5.3 shows the adjusted HR and coefficient for each factor in the final equation. It was observed that CVD risk is increased by 4%, 5%, 11% and 22% for each one unit increase in age, DM duration, HbA1c (%) and total cholesterol, respectively. In addition, patients with albuminuria at baseline were 2.49 times more likely to develop CVD compared to those without albuminuria (95% confidence interval: 1.719–3.601).

Table 5.3

Adjusted hazard ratios and model coefficients for the first cardiovascular event

Predictor	**HR (95% CI)**	**Coefficient (SE)**	***P* value**
Age (per 1 year)	1.04 (1.019 – 1.057)	0.038 (0.009)	< 0.001
DM duration (per 1 year)	1.05 (1.006 – 1.104)	0.052 (0.024)	0.03
HbA1c (per 1%)	1.11 (1.033 – 1.190)	0.102 (0.036)	0.004
Total cholesterol (per 1 mmol/l)	1.22 (1.058 – 1.413)	0.201 (0.074)	0.007
Albuminuria (present vs. absent)	2.49 (1.719 – 3.601)	0.912 (0.189)	< 0.001
HTN (present vs. absent)	1.18 (0.787 – 1.770)	0.166 (0.207)	0.42
BMI (per 1 kg/m^2)	1.005 (0.970 – 1.042)	0.005 (0.018)	0.78

Abbreviations: HR, hazard ratio; CI, confidence interval; SE, standard error; DM, diabetes mellitus; HbA1c, glycosylated hemoglobin; HTN, hypertension; BMI, body mass index.

Moreover, the 5-year baseline survival function (S_0) generated using the Cox regression analysis was 0.9991. Figure 5.1 shows the CVD hazard function at means of all covariates. The increase in the CVD risk seemed gradual and

steady over time. However, it increased sharply after approximately 1 year (330 days), 3.5 years (1270 days) and 5.8 years (2120 days) of follow up. Log – log function lines according to various factors showed almost parallel lines, indicating the satisfaction of the Cox proportional hazards assumption. As examples, Figure 5.2 shows the log – log functions according to HbA1c (A) and albuminuria (B) status respectively and suggests that the hazard ratio for the two categories in each of the two variables are constant over time. The -2 log likelihood statistic changed significantly from the baseline model to the final model. In the final model for which all associated predictors were included, the - 2 log likelihood statistic changed from 1,769 at baseline to 1,690, with a *P* value of < 0.001.

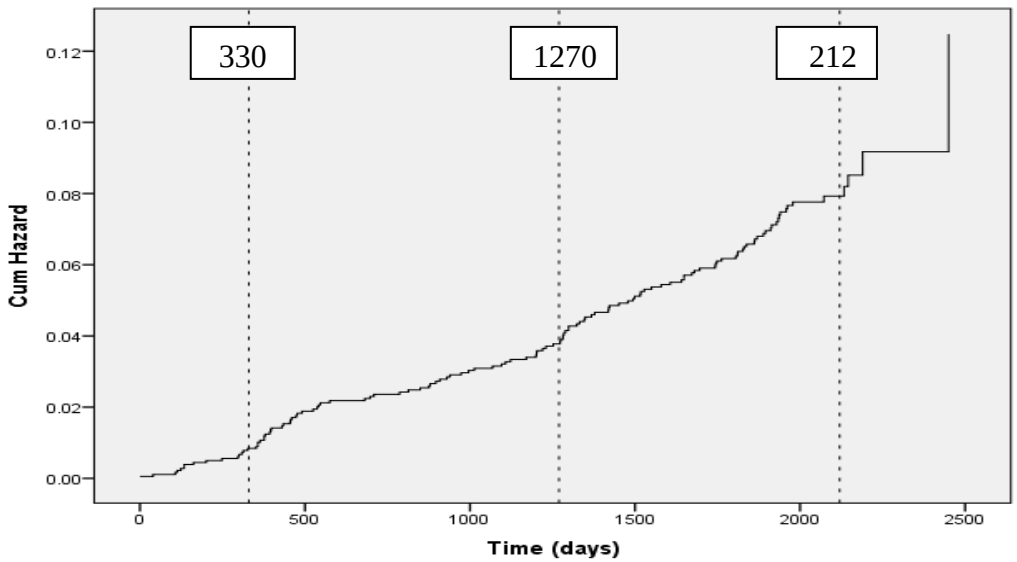

Figure 5.1

Cardiovascular disease cumulative hazard function at mean of covariates

Based on the Cox model coefficients presented in Table 5.3, and the baseline survival function, the 5-year probability of CVD equaled $1 - 0.9991^{Exp\sum XiBi}$, where *Exp* $\sum XiBi$ (which represents the hazard ratio) = *Exp* (0.038 age [years] + 0.052 DM duration [years] + 0.102 HbA1c [%] + 0.201 total cholesterol [mmol/l] + 0.912 albuminuria [coded 1 if present] + 0.166 HTN [coded 1 if present] + 0.005 BMI [kg/m^2])

As an example, the 5-year CVD probability can be calculated in the following steps for a patient with the following profile: age of 50 years, DM duration of 6 years, HbA1c of 7%, total cholesterol of 5 mmol/l, albuminuria present (1), HTN absent (0), BMI of 24 kg/m^2:

$\sum XiBi$ = 0.038 x 50 + 0.052 x 6 + 0.102 x 7 + 0.201 x 5 + 0.912 x 1 + 0.166 x 0 + 0.005 x 24 = 1.90 + 0.31 + 0.71 + 1.01 + 0.912 + 0 + 0.12 = 4.96

Then, $Exp \sum XiBi = Exp\ 4.96 = e^{4.96} = 142.6.$

Then, $0.9991^{142.6} = 0.8795.$

Finally, the CVD risk = $1 - 0.9991^{Exp\sum XiBi} = 1 - 0.8795 = 0.1205$, or 12.05 %.

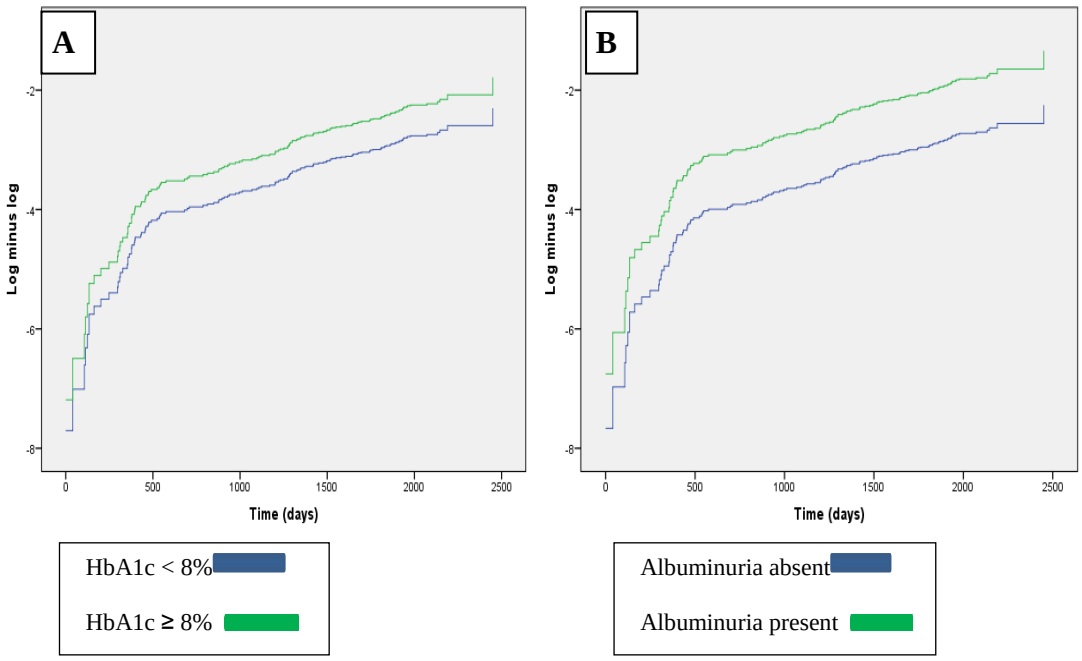

Figure 5.2

Log – log for the cardiovascular disease hazard function according to HbA1c status (A) and albuminuria status (B)

5.5 Discussion

This study was designed to pave the way for the development of a suitable risk assessment tool for the Omani type 2 diabetic population. As such, the first CVD risk assessment tool in the Arab world for Omanis with type 2

diabetes was developed. While many CVD risk assessment models have been established for type 2 diabetics globally, most of these tools have been derived from Western populations (especially European and U.S. populations). In addition, very few of these tools were validated externally. Furthermore, validation studies demonstrated that these tools performed poorly when applied to populations of different ethnicities [20-22]. The results of this study can be utilised for more targeted CVD risk management strategies among diabetic patients in Oman and, perhaps, can be considered for use in neighbouring Arab countries. Moreover, the presented model is the most up-to-date in comparison to some of the global tools [8,9], and reflects current settings in which changes in the management of diabetic patients have occurred over the past few years.

In terms of considered predictors and outcome, the present model included seven CVD predictors and incorporated CHD, stroke and PAD in the CVD outcome. The total number of included factors have varied considerably across other studies. For example, the UKPDS risk engine included seven predictors while the ADVANCE model included 10 predictors [5,9]. In the present study, certain common risk factors such as smoking and HTN, were insignificantly associated with CVD. However, these factors were also excluded by other global models [5,6,7]. This variation could be explained partially by differences in data quality across studies. However, diversity in the patterns of various risk factors and CVD in populations with different lifestyles, cultures and environments may be a better explanation [23]. In this regard, the cumulative incidence of CVD in this study was 9.4% (192/2039) over a median period of 5.6 years of follow-up, which is much higher than the observed incidence in some populations and much lower than others. For example, studies in general practice settings in Scotland and Italy showed cumulative incidence of 5.3% and 7.6% within median periods of 4.1 and 4 years respectively [24,25], while in England and New Zealand it was 17.9% within an almost similar median period of follow-up for both [26,27]. In addition, the prevalence of current smoking as one of the traditional CVD factors was considerably much lower in this study sample compared to global data [5,7,26,27]. On the other hand, the present study included three

components for CVD outcome; this enables physicians to estimate general CVD risk rather than the risk of CHD, stroke or PAD alone. Several international tools like the ARIC, UKPDS, the Chinese Total CHD Risk Score and the Diabetes Audit and Research in Tayside, Scotland (DARTS) study model did not consider stroke and PAD in the CVD outcome [7-9, 24].

Compared to the WHO/ISH risk prediction charts currently used to assess CVD risk among diabetics in primary care institutions in Oman [28,29], the present model was derived from an original longitudinal study using incidence as the outcome measure, whereas the WHO/ISH charts were derived using databases related to the prevalence of CVD risk factors and rates of CVD events in the Eastern Mediterranean region [10]. The latter tool is not specific for the Omani diabetic population as it uses data from a much larger region which includes both Arab and non-Arab populations. Additionally, the WHO/ISH charts do not consider HbA1c and DM duration as key factors, although these variables are important CVD predictors among diabetics. Furthermore, the present model can be converted into electronic software which will be easier to use in clinical practice. However, further validation studies are required to evaluate the accuracy of the present model and its applicability to Omanis with type 2 diabetes.

The present study has some limitations. Although it involved an adequate sample size, a larger sample size taken from different regions is preferred to produce a more accurate model in population studies. Although the Omani population in different provinces shares similar culture and lifestyle, some important differences still exist in few provinces, especially the Dhofar Province, where significantly higher prevalence of obesity and smoking are observed compared to other provinces [12,30]. Therefore, this may limit the generalizability of the mode. However, the present model is still of a great value to the Omani population. In addition, the involved sample size in this study was larger than that used in the development of some of the aforementioned global tools, such as the Australian model [6]. Second, due to limited resources, this study was unable to address some important CVD risk factors such as physical inactivity and use of anti-hypertensive and anti-

diabetic treatments. However, due to the difficulty in gathering and quantifying data related to physical inactivity, most existing global tools also do not address this factor. In addition, the effect of physical inactivity would have been partially accounted for in various other modifiable risk factors addressed in the current study, such as dyslipidaemia, glycaemic control, BP control and obesity. Similarly, the effect of use of anti-hypertensive and anti-diabetic treatments would have overlapped the effects of glycaemic (HbA1c) and BP control addressed in this study.

5.6 Conclusion

This study developed the first CVD risk assessment tool in the Arab world for Omanis with type 2 diabetes. It has the potential to be used by physicians and health planners as an alternative to the WHO/ISH risk prediction charts to estimate the 5-year CVD risk and future disease burden among Omanis with type 2 diabetes. However, further validation studies are necessary to evaluate the applicability of this model among Omanis with type 2 diabetes**.**

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Competing interests

No conflict of interests was involved in this work.

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Chapter 6: (Paper 4) Validation of the Cardiovascular Risk Model Developed for Omanis with Type 2 Diabetes

6.1 Introduction

The last chapter addressed the second research question relating to developing a suitable CVD risk assessment tool for Omani type 2 diabetics. A model was created using seven common risk factors to estimate CVD risk for Omani diabetics. However, the developed model needed to be validated to allow further application. Therefore, this chapter addresses the third research question relating to the validity of the developed model. In this chapter, the validity of the CVD risk assessment model is tested with the model derivation sample (i.e. the sample which was used to develop the model), as well as an external sample. The performance of the model in both the derivation sample and separate validation sample is presented in this chapter.

This chapter is presented as a co-authored original manuscript following the formatting/style requirements of *'Primary Care Diabetes'* journal. However, the pages, sections, figures and tables are re-numbered to be consistent with the flow of the thesis. The bibliographic details of the co-authored paper, including all of the authors, are

Al Rawahi AH, Lee P. Validation of the cardiovascular risk model developed for Omanis with type 2 diabetes. Manuscript ready to be submitted for publication to *'Primary Care Diabetes'* journal. 2017

This chapter commenced with a declaration of authorship followed by an abstract of the article. Then, it presents the details of the study including the methods used, detailed results, a discussion and a conclusion. Finally, a list of references related to the article is given at the end of this chapter.

Declaration

I am (the candidate) the first and the corresponding author of this paper. My contribution to the paper involved: conception of the research idea, reviewing the literature, designing the research methods, supervising the data collection and data entry, analysing and interpreting the data, drafting and reviewing the manuscript. This contribution is acknowledged by all co-authors.

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Validation of the Cardiovascular Risk Model Developed for Omanis with Type 2 Diabetes

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6.2 Abstract

Introduction

The first cardiovascular risk assessment model in the Arab world was recently developed for Omanis with type 2 diabetes mellitus. This study aims to validate the newly developed model.

Methods

A retrospective cohort study design was applied in this study. The model was validated in two samples; the model derivation sample and a separate validation sample, consisting of 1314 and 405 diabetics respectively. All patients were free of cardiovascular disease at the baseline (2009-2010) and were followed up until: the first cardiovascular event occurred; the patient died; or up to December 2015. All data were retrieved from the patients' medical records in a primary care setting.

Results

In both the derivation and validation samples, the model showed good discrimination, with an area under the receiver operating curve of 0.73 (95% CI; 0.69 – 0.77) and 0.70 (95% CI: 0.59 – 0.75) respectively. Calibration of the model was satisfactory and the actual difference between the mean predicted and observed risk in different risk groups ranged from 0.7% - 3.1% and 0.1% - 4.2% in the derivation and validation samples respectively.

Conclusion

The recently developed cardiovascular disease risk assessment model for Omanis with type 2 diabetes achieved adequate overall validity. The model showed good discrimination and acceptable calibration; it therefore has the potential to be used in local clinical settings. However, further validation and comparison studies are needed to judge the generalisability and superiority of the model over other tools currently used in Oman.

Key words: Cardiovascular disease; Risk prediction; Model validation; Type 2 diabetes; Arab populations; Oman.

Highlights

- This paper demonstrates the validation of the first cardiovascular risk assessment tool developed in the Arab world.
- The model showed good discrimination and calibration, supporting its application among Omani diabetics.
- The model may be used by physicians to estimate CVD risk among type 2 diabetic patients in order to optimise patient care.

Introduction

Risk assessment tools in general are mathematical models or charts used to estimate the risk of a condition/outcome event for an individual. They are usually based on the predictive information available for various risk factors of a specified outcome. In these models, the standardised coefficient of each included risk factor indicates its relative contribution to the overall risk of a given health condition [1-3].

In the context of cardiovascular disease (CVD) prevention and management, such models are usually used to estimate an individual's CVD risk, which can then be used to assess the prognosis and support the choice of preventive and therapeutic strategies for individuals at risk. Once an individual's CVD risk is predicted with some degree of certainty, management can be tailored accordingly, such as when to intensify a preventive intervention, when dietary advice needs to be specific, when advice on physical activity needs to be intensified and individualised and when specific drugs need to be prescribed to control CVD risk factors [4].

The use of CVD risk assessment models among type 2 diabetics using traditional CVD risk factors such as hypertension (HTN), dyslipidemia, high glycosylated hemoglobin (HbA1c), albuminuria, obesity, smoking status, and family history of CVD has been emphasised in several professional guidelines [5,6]. A few examples of such global tools include: the U.K Prospective

Diabetes Study (UKPDS) risk engine for diabetes patients; the Action in Diabetes and Vascular Disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) study model; the Australian Fremantle Diabetes Study (FDS) model; the U.S Atherosclerosis Risk in Communities (ARIC) model; the World Health Organization /International Society of Hypertension (WHO/ISH) charts and the Chinese Total CHD Risk Score [7-12].

As the above global models are not optimal for populations with different lifestyles and ethnicities [13], the first CVD risk assessment model in the Arab world was recently developed in the form of a mathematical equation using seven common traditional CVD risk factors for Omanis with type 2 diabetes mellitus (DM) [14]. The estimated 5-year CVD probability according to this model is expressed as $1 - 0.9991^{Exp\sum XiBi}$, where $Exp\ \sum XiBi = Exp$ (0.038 age [years] + 0.052 DM duration [years] + 0.102 HbA1c [%] + 0.201 total cholesterol [mmol/l] + 0.912 albuminuria [coded 1 if present] + 0.166 HTN [coded 1 if present] + 0.005 BMI [kg/m^2]). In addition, the CVD outcome considered in this model includes coronary heart disease (CHD), stroke and peripheral arterial disease (PAD), enabling treating physicians to estimate overall CVD risk. However, this model has not yet been validated. In order to extend the use of this recently developed model as a feasible CVD risk assessment tool in clinical practice and to ascertain the suitability of the model, this study aimed to validate this CVD model developed for Omanis with type 2 DM.

6.3 Methods

Study design and participants

The performance of the model was evaluated with two samples: the model derivation sample and another independent sample (validation sample). The derivation sample was selected from four primary care institutions in the Aldakhilyah Governorate (Province) of Oman, and was used to develop the model; while the validation sample was taken from other two primary care institutions in the same Province. A retrospective cohort study design was utilised for both the internal and external validation of the model. The

derivation sample included 1,314 Omani type 2 diabetic patients from three polyclinics (Nizwa, Bahla, and Izki Polyclinics) and one large health center (Manah Health Centre). The reference population and the health care settings from which the derivation and validation samples were taken have been described elsewhere [14]. The validation sample consisted of 405 patients chosen from one polyclinic (Samail Polyclinic) and one health centre (Burkat Almoz Health Center). The year 2009–2010 was considered to constitute the baseline for this study.

The same sampling methods, inclusion/exclusion criteria and variable/outcome definitions that were used for the derivation sample were also applied to the validation sample [14]. In brief, all Omanis with type 2 diabetes who were recorded in the diabetes registry of the selected institutions and were free of CVD at baseline were included in the study. The included patients were followed up until either their first CVD outcome occurred they patient died or until the end of the data collection period in December 2015. The exclusion criteria were defined as follows: patients with incomplete data related to key CVD factors and outcomes at baseline and those who developed heart diseases or underwent limp amputations due to non-ischaemic causes during the follow-up period. In addition, patients with end-stage renal disease and liver cirrhosis were also excluded.

Data collection

In both samples, data on demographic characteristics, key risk factors at baseline and CVD outcomes were gathered by trained staff using a well-designed data collection sheet. The data were retrieved from the diabetes registers and patients' computerised files at the selected institutions. All definitions of variables in the present study were consistent with those used in the previous model derivation study

The CVD outcomes included fatal and non-fatal CHD, stroke and PAD events. These outcomes were recorded from baseline (2009–2010) until December 2015 (a maximum follow-up period of 7 years), by reviewing clinical diagnoses and physician's clinical notes documented at all patients’ visits during this

period. Descriptions of the CVD diagnostic criteria and risk factor definitions have been presented elsewhere [14]. In brief, CHD was diagnosed based on clinical presentation and confirmed by electrocardiography, a troponin test, a treadmill test and/or coronary angiography. A stroke event was confirmed by a computed tomography scan and PAD was confirmed by either a clinical diagnosis of gangrene, a limb amputation due to an ischaemic cause or intermittent claudication confirmed by angiography. In addition, causes of death were also determined from death certificates.

In terms of CVD risk factors, albuminuria was defined as an albumin/creatinine ratio of ≥2.5 for males and ≥3.5 for females confirmed at least twice within three months or longer, after excluding other possible causes. A HTN diagnosis was defined as multiple readings of systolic blood pressure of ≥140 mmHg or diastolic blood pressure of ≥90 mmHg, after excluding other causes of elevated blood pressure [15,16]. In addition, total serum cholesterol and HbA1c were measured using standardised laboratory equipment. All laboratory measurements and definitions were consistent with those used in the model derivation study [14].

Data analysis

Data analysis was performed using SPSS software, Version 22.0. Continuous variables were expressed in means and standard deviations (SDs), while categorical variables were presented in total counts and percentages. The general performance of the model in the derivation sample was assessed using the -2 log likelihood statistic and by comparing the overall mean predicted CVD risk to overall mean observed risk. The ability of the model to discriminate CVD risk in both samples was assessed by calculating the area under the receiver operating curve (ROC) with 95% confidence intervals (CIs). Calibration of the model was assessed by comparing the mean predicted CVD risk and the mean observed risk in the fifths (quintiles) of the predicted risk with a Hosmer-Lemeshow (HL) Chi-squared test [17,18,19]. For this test, each sample was split into five groups (quintiles) of equal size, by sorting the predicted risk in descending order so that the first 20% of patients represented the group with the lowest CVD risk. Moreover, the Brier score (mean squared

error with score range) was calculated to assess the accuracy of the model in each sample. Sensitivity, specificity, likelihood ratios and positive and negative predictive values for cut-off CVD risk values of 5%, 10% and 15% were also obtained to determine the optimal cut-off point [20,21]. In addition, the optimal statistical cut-off value of CVD risk was identified whereby the sum of the sensitivity and specificity values yielded the largest value.

This study was ethically approved by the Regional Research and Research Ethics Committee of the Ministry of Health in Oman and the Griffith University Research Ethics Committee.

6.4 Results

Table 6.1 compares baseline CVD predictors between the derivation and validation samples. Mean follow-up periods among the derivation and validation samples were 5.3 and 5.6 years (*P* <0.001), respectively, with a minimum and maximum follow-up period of zero and 7 years in both groups.

Table 6.1

Baseline predictors and cardiovascular outcome among the derivation and validation samples

Characteristic	**Derivation sample (n=1314) % or mean ± SD**	**Validation sample (n=405) % or mean ± SD**	***P* value**
Sex (female)	64.1%	64.0	0.96
Age (years)	55.3 ± 11.0	52.3 ± 11.4	< 0.001***
DM duration (years)	6.6 ± 4.0	5.3 ± 4.1	< 0.001***
Total cholesterol (mmol/l)	4.9 ± 1.1	5.2 ± 1.2	< 0.001***
HbA1c (%)	7.9 ± 2.2	8.1 ± 2.2	0.03*
BMI (kg/m^2)	29.1 ± 5.3	28.3 ± 5.0	0.01*
Albuminuria (present)	18.6%	22.2 %	0.10
HTN (present)	58.6%	50.9 %	0.01*
CVD outcome (present)	9.6%	12.8 %	0.06

Abbreviations: SD, standard deviation; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; BMI, body mass index; HTN, hypertension; CVD, cardiovascular disease

Approximately 64% were female in both groups. The derivation sample was slightly older than the validation sample (55.3 ± 11.0 years vs. 52.3 ± 11.4 years; *P* = 0.001). Over the study period, 9.6% (126/1,314) vs. 12.8% (52/405) CVD events were observed among the derivation and validation samples, respectively, with no statistically significant difference between the two groups (*P* = 0.06).

Performance of the model in the derivation sample

In the derivation sample, the -2 log likelihood statistic changed significantly from the baseline model to the final model; including all predictors, the -2 log likelihood statistic changed from 1,769 to 1,690 (*P* <0.001). The overall predicted mean risk was 11.5% compared to the observed mean risk of 9.6%. The ROC for the predicted CVD risk by the model in the derivation sample is shown in Figure 6.1 (A). The area under the curve (AUC) was 0.73 (95% CI: 0.69–0.77).

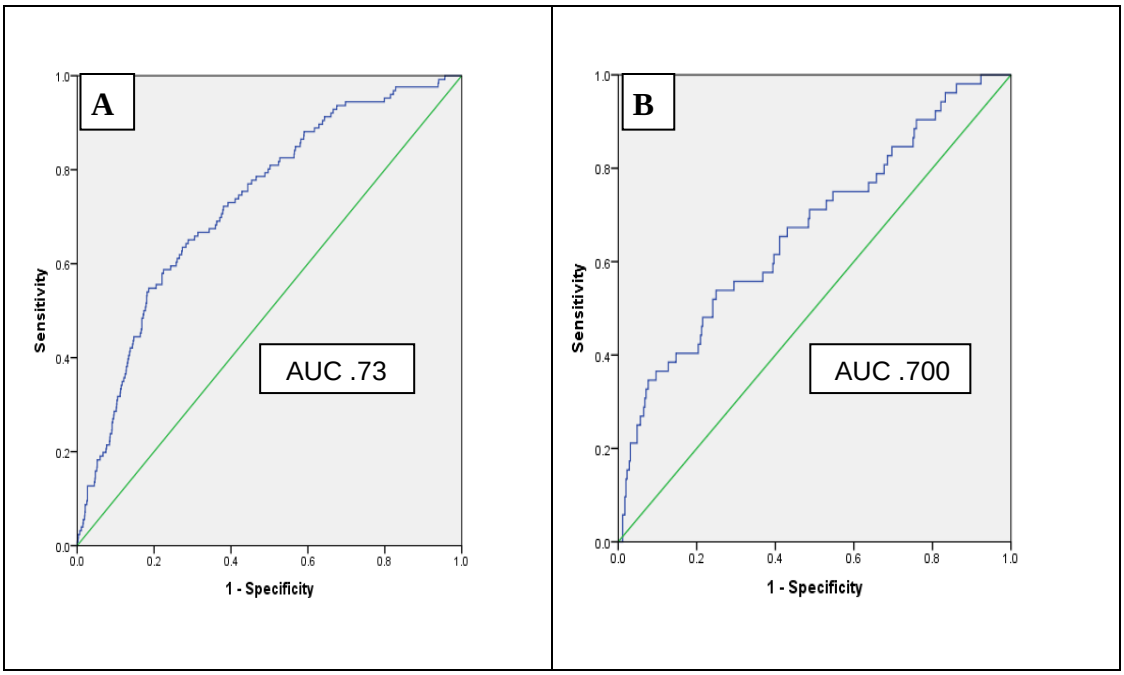

Figure 6.1

Receiver operating curves for the 5-year cardiovascular risk prediction model among Omani type 2 diabetics, in the study sample (A) and in the validation sample (B)

The calibration of the model in the derivation sample is shown in Figure 6.2. The HL Chi-square test showed no significant difference between the predicted and observed risk across the five groups (*P* = 0.15). The predicted levels of risk tended to slightly overestimate the CVD risk by 0.7 – 3.1% in the sample.

In the derivation sample, the Brier score was 0.08 (range: 0–0.74). The optimal statistical cut-off point (whereby sensitivity plus specificity yielded the greatest sum) was identified at a predicted risk of 0.116 (11.6%), with a sensitivity of 66.7% and a specificity of 68.6%. Table 6.2 presents the sensitivity, specificity, predictive values and likelihood ratios at different cut-off values. A cut-off CVD risk value of 10.0% yielded a sensitivity of 73.0% and specificity of 60.3%. However, specificity at the cut-off value of 5% appeared to be very low (24.2%). On the other hand, low sensitivity (54.8%) was observed at the cut-off value of 15%.

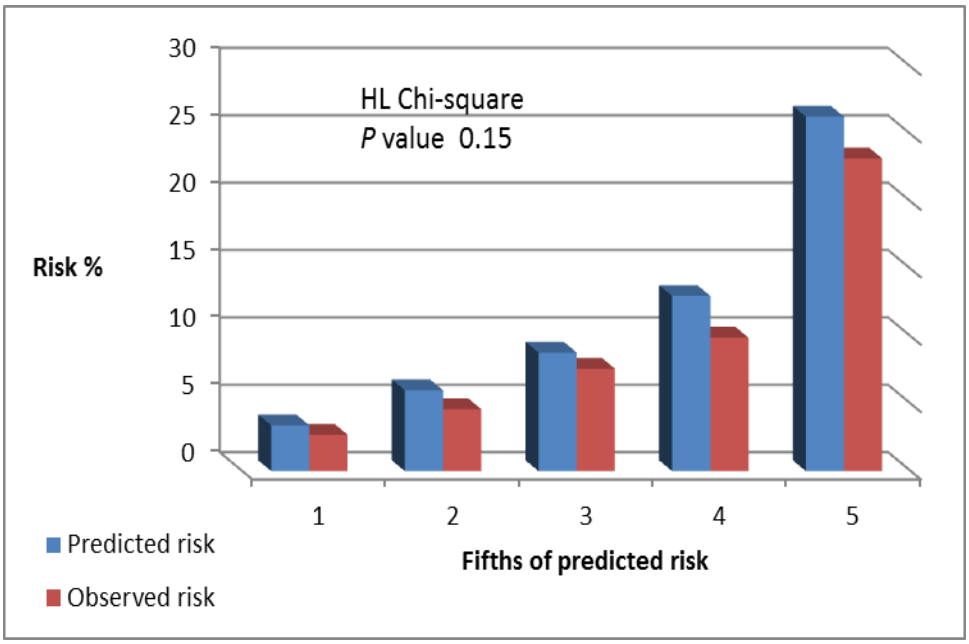

Figure 6.2

Predicted vs. observed cardiovascular risk in each of the fifths of the derivation sample

Performance of the model in the validation sample

Among the validation sample, the overall mean predicted risk was 11.0% compared to the overall observed CVD risk of 12.8%. Figure 6.1 (B) shows the ROC curve in the validation sample with an AUC of 0.70 (95% CI: 0.59 – 0.75). Regarding the calibration of the model in the validation sample, Figure 6.3 compares the mean predicted and observed CVD risks in the fifths of the validation sample. The actual difference between the mean predicted and observed risk in different risk groups ranged from 0.1% - 4.2% in the validation sample. The predicted risks were slightly underestimated in the first three quintiles but overestimated in the fourth quintile. However, the HL Chi-square test showed no significant difference between predicted and observed risks in the five groups (*P* = 0.06). In addition, the Brier score was 0.1 (range: 0–1) in the validation sample.

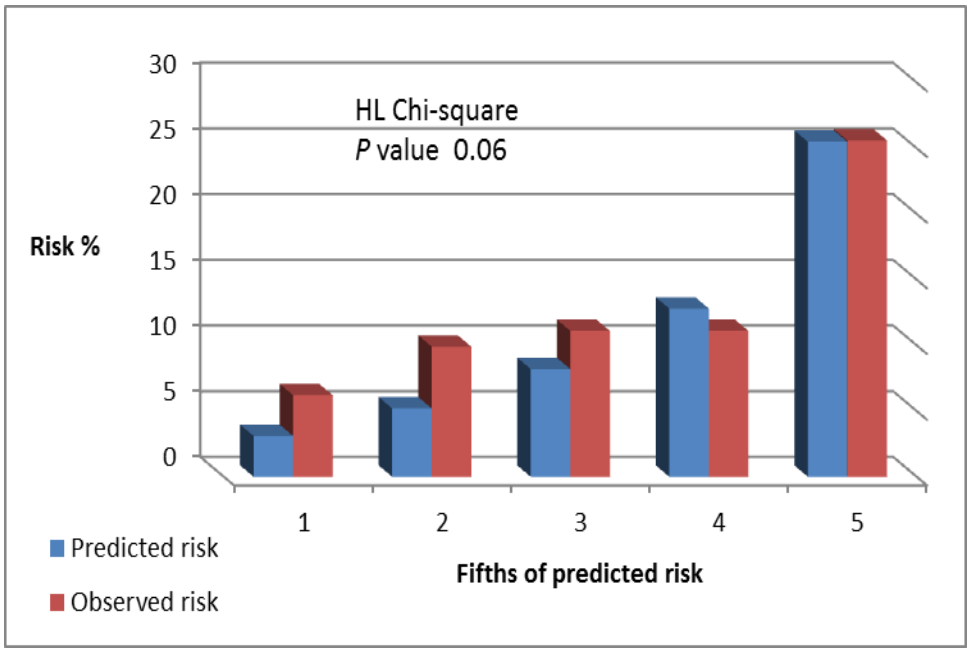

Figure 6.3

Predicted vs. observed cardiovascular risk in each of the fifths of the validation sample

6.5 Discussion

This study indicated that the recently developed CVD risk assessment model for Omanis with type 2 diabetes achieved adequate overall validity. The model showed good discrimination and calibration in both the derivation and validation samples.

However, the ability of the model to predict CVD risk based on the area under the ROC was higher in the derivation sample than the validation sample, which is expected as the model was developed based on the former sample. However, an AUC value of 0.70 in the external validation sample indicates a good result arising from a different sample [8,22,23,24].

Table 6.2

Sensitivity, specificity, predictive values and likelihood ratios of the model at different cut-off values of predicted CVD risk in the derivation sample

Risk (%) cut off point	Sensitivity (%)	Specificity (%)	Predictive value +ve (%)	Predictive value –ve (%)	Likelih-ood ratio +ve	Likelih-ood ratio -ve
5.0	94.4	24.2	11.7	97.6	1.25	0.23
10.0	73.0	60.3	16.3	95.4	1.84	0.45
11.6**	66.7	68.6	18.4	95.1	2.12	0.49
15.0	54.8	80.1	22.6	94.3	2.75	0.56

Note: **, the optimal statistical cut off point

Similarly, the model calibration results showed a good outcome in comparison to other tools in the literature [9,17,23]. Although there was a slight overestimation of CVD risk in the derivation sample, there was a slight underestimation in risk in the validation sample. The slight underestimation of CVD risk in the validation sample observed in the first three quintiles may represent a small proportion of high-risk patients missed by the model. On the other hand, the slight overestimation of CVD risk in the fourth quintile could

represent false-positive cases identified by the model. However, the proportion of risk underestimation/overestimation in the both samples was small and not statistically significant according to HL Chi-squared test results.

The Brier scores indicated very good results in terms of the accuracy of the model in estimating CVD risk in both samples, since the scores fell on the lower side of its ranges for both samples (derivation sample: 0.08, range: 0–074; validation sample: 0.1, range: 0–1). The optimal statistical CVD risk cut-off value was observed at 11.6%, with good sensitivity (66.7%) and specificity (68.6%). However, a higher sensitivity (73.0%) and lower specificity (60.3%) were observed at a cut-off value of 10% compared to the cut-off value of 11.6%. Moreover, the cut-off value of 11.6% yielded a higher proportion of false-negative patients compared to the cut-off value of 10.0%, which yielded more false-positive patients. As such, a cut-off value of 11.6% is expected to omit many true-positive cases (i.e. high-risk patients), which is clinically unfavourable. On the other hand, no harm would be caused if a low-risk patient is mistakenly classified as high-risk (i.e. false-positive cases). Therefore, a cut-off value of 10.0% is preferable in clinical application.

Although the negative predictive values of the model were very good at all suggested cut-off points (>95%), the positive predictive values (PPVs) were consistently low. However, similar results have been observed in other international models. A low PPV is to be expected as these models are used for screening and not for diagnostic purposes [9,12,24]. The major effect of a low PPV is that it may result in a high proportion of patients receiving false-positive results. Patients with false-positive results (incorrectly classified as having a high CVD risk) will simply be advised to adjust their lifestyles and dietary habits, and may receive a pharmacological preventive measure, all of which are safe and will not incur significant medical costs.

Although the two samples involved in this study were drawn from the same reference population and had a comparable gender distribution and insignificant differences in CVD incidence, the two samples differed in many other characteristics, such as mean age, DM duration and HTN prevalence. However, this may reflect the actual variations in two independent samples,

which is expected in external validation studies. Despite these differences, the model performed well in the validation sample and the results support the generalisability of the model among Omani type 2 diabetics.

In general, the performance of any model depends on many factors related to the study design, such as the sample size, quality of data, statistical methods used, total variance in CVD outcome explained by the predictors and the number of predictors included in the model [25]. The present study was strengthened by a cohort study design and a sample of sufficient size. In addition, the derivation sample was deemed to be representative of the target population and the Cox regression modelling method used in this study is best suited for such longitudinal data. Moreover, the primary data were of good quality since they were obtained by professional staff working in clinical settings and following standardised data management procedures. Based on these factors, in addition to the satisfactory validation results achieved in this study, the present model is considered to be appropriate for application in clinical settings and diabetes care centres in Oman.

6.6 Conclusion

This study validated the first CVD risk model developed for Omanis with type 2 diabetes. The validation of the model was achieved using a derivation sample among which the CVD risk assessment model was originally developed as well as a separate sample drawn from the same diabetic population. Overall, the model showed good performance with adequate discrimination and acceptable calibration. It is suitable for application in Omani clinical settings. However, further validation and comparison studies are needed to evaluate the present model in comparison with other tools currently used in Oman in order to generalise the present model to wider populations.

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Competing interests

No conflict of interests was involved in this work

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Chapter 7: Discussion and Conclusions

7.1 Introduction

The previous result chapters of this study (presented as individual co-authored papers) were organised in a logical sequence in order to answer the research questions of this research project. As part of the journal articles, each of the chapters included a separate discussion section that addressed explanations of various observed results, comparisons of the findings in relation to the literature, strengths and limitations of the used methods and implications of the findings in current practices. However, this chapter takes a wider view on how the three studies in combination have addressed the aim and objectives of the entire project, the implications of the main findings and the addition of information to the existing literature resulting from this thesis. The strengths and limitations of the whole research project are also discussed in this chapter. In addition, general conclusions and recommendations for future research are addressed.

Many cardiovascular disease (CVD) risk assessment tools have been developed globally to estimate CVD risk among type 2 diabetics. However, to date, no studies aiming to develop specific risk assessment tools for Arab populations, including Omanis, have yet been conducted. This thesis commenced by critically reviewing the applicability of existing global CVD risk assessment tools to the Omani type 2 diabetic population. The findings of a literature review suggested that these tools are not optimal for this population. Therefore, the ultimate goal of this project was to develop a suitable CVD risk assessment tool for Omani type 2 diabetics. This was achieved by conducting three consecutive sub-studies (presented in Chapters 4 to 6), each addressing one of the following three research questions:

1- What is the incidence of CVD and the pattern of CVD risk factors among type 2 diabetics in Aldakhiliyah Province of Oman?

2- How can associated CVD risk factors be incorporated into a multivariate model for predicting the five-year risk of CVD in the type 2 diabetic population in the Aldakhiliyah Province of Oman?

3- How valid is the developed risk assessment model to predict the five-year CVD risk in another cohort of type 2 diabetics taken from the same reference population?

The following section highlights the main findings which have been presented and discussed in detail in the last three chapters (Chapters 4 to 6). A broader discussion related to the growing burden, implications and potential long-term impacts of CVD and CVD risk factors in the Omani type 2 diabetic population is addressed subsequently. In addition, a general discussion related to the developed CVD risk assessment model and its implications in clinical practice is also presented. Moreover, this section elaborates on the implications of the model validation results and recommendations for the further generalisability and feasibility of the model for application in clinical settings.

7.2 Key findings of the study

The following key findings in the three individual studies were observed. In the first study, the overall incidence of CVD among Omani type 2 diabetics was 9.4% over a mean period of 5.3 years, and the annual incidence ranged from 0.7% to 2.1%. On the other hand, a high prevalence of key CVD risk factors, such as poor glycaemic control, hypertension (HTN), obesity, dyslipidaemia, and albuminuria was observed. In addition, a crude analysis revealed the following seven factors to be significantly associated with CVD: age; diabetes mellitus (DM) duration; body mass index (BMI); glycaemic control; HTN; total serum cholesterol; and albuminuria. However, insignificant associations were observed between CVD and other known risk factors such as gender, smoking status and a family history of CVD.

The second study revealed five independent factors to be associated with CVD: age, DM duration, glycosylated haemoglobin (HbA1c), total cholesterol and albuminuria. Although HTN and BMI were excluded by the multivariate

analysis, these factors were included in the final CVD probability equation since they were associated with CVD in the crude analysis and were entered in the Cox regression method. In this regard, the five-year probability of CVD among Omani type 2 diabetics was modelled as: $1 - 0.9991^{Exp\sum XiBi}$, where *Exp* $\sum XiBi$ (which represents the hazard ratio) = *Exp* (0.038 age + 0.052 DM duration + 0.102 HbA1c + 0.201 total cholesterol + 0.912 albuminuria [coded 1 if present] + 0.166 HTN [coded 1 if present] + 0.005 BMI).

In the third study, the model performed well when validated in both the sample used to derive the model as well as a separate validation sample. The model was validated by calculating the area under the curve (AUC) of the receiver operating curve (ROC) for discrimination and using the Hosmer-Lemeshow (HL) Chi-squared test for calibration. The results indicted good discrimination, with AUC values of 0.73 (95% confidence interval [CI]: 0.69–0.77) and 0.70 (95% CI: 0.59–0.75) observed in the derivation and validation samples, respectively. In addition, the model showed good calibration (*P* = 0.15 and 0.06 in the derivation and validation samples, respectively), with the actual difference between mean predicted and observed risk in five different risk groups ranging from 0.7–3.1% and 0.1–4.2% in the derivation and validation samples, respectively. In addition, the model yielded good sensitivity (73.0%) with reasonable specificity (60.3%) at a CVD risk cut-off value of 10.0% to identify high-risk patients.

7.3 CVD incidence and patterns of CVD risk factors

The first study in this project answered the first research question related to CVD incidence and risk factor patterns among Omani type 2 diabetics. In response to this question, a retrospective cohort study was conducted using a representative sample of 2,039 Omani type 2 diabetic patients selected from several primary care settings specialising in diabetes care in Al Dakhiliah Governorate. Data on CVD risk factors were collected at baseline (2009–2010) and patients were followed up from baseline until their first CVD outcome, their death or until the end of the follow-up period in December 2015. All data were retrieved from patients' medical records and the National Diabetes Registry. This study is novel as no previous studies have explored

the incidence of CVD and profile of CVD risk factors among a cohort of diabetic patients in Oman.

This study found that the CVD incidence among the type 2 diabetic population in Oman is high. However, global CVD incidence rates vary according to definitions of CVD outcomes, length of follow-up period and sample characteristics and settings. In this context, the CVD cumulative incidence among type 2 diabetic patients was reported to be 4.3% and 5.3% in China and Scotland, respectively, while it was reported as 17.1% and 20.2% in the U.S. and Finland, respectively.[95,103,142,144,239] Nevertheless, global trends in CVD and CVD-related risk factors seems to be increasing over the last few decades. For example, the prevalence of obesity has risen notably over the past three decades, from just a few percent to around 30% in some countries; the prevalence of type 2 diabetes has also risen steadily.[251] This is consistent with global trends, especially in developing countries where the situation is more challenging.[252]

The results of this study indicate an essential milestone in the measurement of CVD events over time among diabetics in Oman and the Arab region. These incidence data will contribute to the long-term monitoring of CVD burden among diabetic populations in the region and provide baseline data for future epidemiological studies in similar fields.

In addition to the potential burden of CVD among the Omani diabetic population, the high prevalence of key risk factors observed in this study, in line with the results of other local studies,[18,201] also reflect the increasing burden of CVD and CVD-related risk factors in Oman, which poses a challenge to the national healthcare system. The high prevalence of these risk factors in conjunction with the effect of an ageing population (i.e. increased life expectancy) indicate that the long-term impacts of these risk factors on population health are expected to be even greater. Developing and/or strengthening CVD prevention programmes targeting common risk factors at individual as well as population levels are critical. Otherwise, the increasing trend of CVD will continue, as well as that of other chronic diseases, as certain CVD risk factors (such as high BMI and dyslipidaemia) are common

for other non-communicable diseases.[15–18] Subsequently, this will have a major impact on the needs and costs of local various prevention and therapeutic services in the future.

On the other hand, based on the current patterns of CVD risk factors, treating physicians should anticipate a high CVD risk among Omani diabetics in general. Routine screening for common risk factors in addition to appropriate risk estimation using available risk assessment tools should therefore be emphasised,[230,231] in order to more effectively plan for diabetes management services. In the current primary care settings in Oman, there is a need for appropriate risk assessment, potentially due to the lack of knowledge about the importance of such risk assessment tools and their clinical implications among physicians.[29] Therefore, in order to optimise diabetes care, local health authorities should advocate the importance of using available risk assessment tools by incorporating them into local guidelines and delivering required training.

Several international studies have shown that HTN, dyslipidaemia, glycaemic control, gender, age, physical inactivity, smoking status, albuminuria, DM duration, ethnicity and a family history of CVD are the most commonly identified predictors of CVD among diabetics.[3,101–103,141,143–146] However, the first study in this project revealed important differences in associations between CVD risk factors and CVD outcomes in an Omani type 2 diabetic sample as compared to several global studies.[102,136,141,142,144,187] In this regard, while DM duration, total cholesterol and albuminuria were identified as significant CVD risk factors in this study, they were excluded in similar studies.[102,103,144–146] In contrast, gender, smoking status and a family history of CVD were identified as significant risk factors of CVD in other international studies,[103,142,144,146] but were excluded in the present study. In fact, inconsistent results in terms of CVD risk factors have been observed in different studies globally.[101,102,144,187] Insignificant smoking and family history of CVD could be due to inaccuracies in self-reported data. The diversity in the pattern of associated risk factors may be explained partially by differences in study design, sampling procedures and quality of data. However, it seems that

the profile of CVD risk factors varies in different populations that differ in cultural and social aspects.[253,254] In fact, diverse CVD risk factor profiles are commonly found in different reference populations in existing CVD risk assessment studies. This implies that existing global CVD risk assessment models are population-specific within the context of each study. Hence, the use of these models in a different population may not always be suitable. Therefore, when applying them in any given diabetic population, such CVD risk assessment tools should be used with caution.

Responsible physicians should provide diabetic patients with sufficient information, addressing the importance of multiple risk factors in CVD risk management measures. Taking into consideration glycaemic control, HTN status, albuminuria and other significant factors in CVD risk estimation and management is more reliable than depending on the general physician's personal judgment. This approach enables physicians to plan more focused preventative measures for each individual patient. Such measures may include intensification of physical activity as well as prescription of specific dietary advice and pharmacological therapy.

7.4 The CVD risk prediction model developed in this project

The first study identified potential CVD risk factors in the Omani type 2 diabetic population using crude analysis, in preparation for the development of a risk model via multivariate analysis in the second study. The second study was designed to derive a suitable risk assessment tool for the Omani type 2 diabetic population. The tool was developed in the form of a statistical equation by which the CVD risk of individual patients could be estimated. This was achieved by modelling the five-year CVD probability using Cox regression methods within a retrospective cohort study design. As such, out of the total sample used for the first study, 1,314 Omani type 2 diabetic patients with complete data related to all key risk factors were included in this sub-study. The five-year probability of CVD was modelled as: $1 - 0.9991^{Exp\sum XiBi}$, where *Exp* $\sum XiBi$ (signifying the hazard ratio) = *Exp* (0.038 age + 0.052 DM duration + 0.102 HbA1c + 0.201 total cholesterol + 0.912 albuminuria [coded 1 if present] + 0.166 HTN [coded 1 if present] + 0.005 BMI). Compared with

existing tools, differences were observed in the number and coefficients of the included predictors in the risk model, as well as the considered CVD outcomes.[103,141,222]

In this study, three modifiable risk factors were among the independent significant risk factors for CVD in the study population. These included HbA1c, total cholesterol and albuminuria. As such, these should be given special attention in respect to patient management, since they are modifiable and can be tackled using more targeted preventive measures. Unfortunately, the current high prevalence of these factors, as shown in this project and other local studies, will inevitably lead to an increasing trend of CVD and other diabetes complications as well. Treating physicians should incorporate these factors in diabetic management plans to provide more specific care and health education, as well as strict pharmacological treatments, at individual level. On the other hand, government authorities and public health practitioners can strengthen existing health promotion and education programmes at population level. These CVD prevention programmes should employ a comprehensive approach, addressing multiple risk factors including diabetes, to target both high-risk individuals and the general population. In this regard, programmes addressing lifestyle risk factors—such as promoting physical activity and healthy diets—should be introduced or strengthened to target modifiable risk factors.

Compared to some of the global models,[103,142,144,146] the present model considered CHD, stroke and PAD in the CVD outcome. Considering all three of these entities enables physicians to estimate overall CVD risk rather than the risk of CHD, stroke or PAD alone. In addition, health planners may use the developed risk assessment model to estimate the future CVD burden which is useful to anticipate needed therapeutic and preventive services for all three CVD entities. Moreover, compared to some existing tools, such as the currently used WHO/International Society of Hypertension (ISH) risk prediction charts, the present model is expected to be more specific since it was designed especially for Omani patients, while the WHO/ISH risk prediction charts were derived from data that included both Arab and non-

Arab populations. Additionally, the WHO/ISH risk prediction charts do not consider HbA1c and DM duration as key risk factors, while these variables were found to be important CVD predictors among diabetics in Oman. Moreover, the present model is a newly developed one, while the WHO/ISH risk prediction charts and other global tools have not been updated for over 10 years.[142,146] Therefore, the present model is considered to be more current and advantageous for physicians to estimate CVD risk in individual patients from Aldakhilyah Province, the region from which the involved sample was selected. In addition, health planners may use this model to monitor CVD risk and project the future burden of CVD among Omani diabetics, and hence, anticipate future needs for therapeutic and preventive services.

7.5 Validation of the developed CVD risk assessment model

In the third study, the CVD risk assessment model was validated in the derivation sample used to develop the model and a separate validation sample consisting of 405 patients selected from the same reference population in Aldakhiliah Province. Model discrimination and calibration were assessed mainly using the AUC under the ROC and HL Chi-squared test, respectively. In addition, Brier scores were calculated to further assess the accuracy of the model.

Despite the differences between the derivation and validation samples, the model performed well in both the derivation and validation samples, respectively (AUC: 0.73 and 0.70; HL Chi-squared *P* value: 0.15 and 0.06; Brier score: 0.08 and 0.1). This supports the generalisability of the model to Omani type 2 diabetics, at least among those in the same region. Therefore, piloting this model in clinical practice in the Aldakhiliyah Province would be the main priority for the extension of this project. In this regard, using the model to estimate CVD risk in the existing sample, as well as for newly registered patients, and monitoring annual risk and CVD events will be of a great value in further validating the model and in the clinical management of individual patients.

In addition, at a CVD risk cut-off point of 10.0% in the derivation sample, the model revealed sensitivity and specificity of 73.0% and 60.3% respectively. At this cut-off value, there would be a lower proportion of false-negative results (i.e. the non-identification of patients with a high risk of CVD) compared to the other potential CVD risk cut-off values. On the other hand, treating false positive patients as high risk is not harmful since the preventive interventions are safe. Therefore, 10% is considered the optimal cut-off point recommended for use by treating physicians to identify high-risk patients in clinical practice. Patients with a CVD risk of ≥10.0% should be considered high-risk and should receive necessary preventive measures including both pharmacological and non-pharmacological interventions. In relation to the literature, few studies reported the sensitivity and specificity measures of global models. [12,102,103] In this regard, the Chinese model revealed sensitivity and specificity of 67.6% and 68.5%, while the Framingham model and the UKPDS model revealed sensitivity of 78.5% and 78.95 respectively, and specificity of 36% and 49.7% respectively.[12,103] Therefore, sensitivity of 73% with specificity of 60.3% seems acceptable.

As the risk prediction model was developed in consideration of the combined effect of multiple risk factors, the risk estimation result for each patient can indicate not only the overall level of CVD risk but also the risk factors which contribute significantly to any increased risk of CVD. Accordingly, more specific advice on patient care can be provided for each individual compared to that in current practices of CVD risk assessment in the local settings, which is based mostly on each physician's clinical and personal experience and which cannot establish a specific level of risk for each individual.[230]

On the other hand, the low positive predictive value of the model would be expected to identify a high proportion of patients with false-positive results (i.e. the identification of low-risk patients as having a high risk of CVD). This would unnecessarily increase the cost of diabetes care, mainly in terms of pharmacological interventions, and the number of referrals to other services such as dieticians and health educators. However, delivering known preventive measures (e.g. lifestyle modification advice and anti-lipid, anti-

platelet and insulin therapies) to false-positive patients is not harmful, since all of these measures are clinically safe. Therefore, future studies to evaluate the cost-effectiveness of using this model are highly recommended.

7.6 Overall evaluation of the developed CVD risk assessment model

This model was developed using a retrospective cohort study design which is considered one of the most appropriate designs for this purpose. The involved sample was taken from primary care institutions in the Aldakhiliyah Province of Oman, where all diagnosed type 2 diabetic patients in the region are followed up and managed. In addition, the sample size exceeded the required size indicated by the sample size calculation. Therefore, the sample was representative for the target population. All data were retrieved from reliable data sources, including computerised patient records and the National Diabetes Registry. The patients' clinical and laboratory assessments in the involved institutions were undertaken by trained diabetologists, general practitioners and nursing staff, and the data were collected using standardised forms as per national clinical guidelines. Laboratory equipment in the involved institutions was regularly checked and calibrated.in addition, the fieldwork in this project involved re-checking 10% of the gathered data to ensure the quality of data. In addition, data entry was done using Epi-data entry software in order to reduce data entry errors. Furthermore, the model was derived using the Cox regression method which is better than the classical logistic regression.

With regards to the applicability of the newly developed model in Oman, incorporation of the CVD risk assessment tool into the local healthcare system is relatively simple and feasible, since a computerised medical record system has been already established in almost all healthcare settings. Minimal resources (such as funding and technical support) will be required to convert the CVD risk assessment model into an online accessible tool for relevant healthcare staff. The developed model can also be installed within the existing system as additional software for diabetes care, so that treating physicians will be able to estimate each patient's risk and plan personalised care to prevent

CVD-related complications. Current routine annual assessment of CVD risk factors for type 2 diabetic patients will make the use of this model easy with coordination from the Omani Ministry of Health in local healthcare settings.

In local clinical settings, users of the model should be made aware of the importance of CVD risk assessment and how to use the tool to assess CVD risk. This can be achieved by incorporating the current model in local guidelines and ensuring their wide dissemination to all health institutions. In addition, regular training sessions and workshops on the application of the risk assessment tool are needed for all involved medical staff. However, collaboration with the local health authorities and technical support is required in order to reinforce application of the new tool.

As such, based on the discussion above, this study has demonstrated that the new model is valid, reliable, suitable and applicable for the target population. However, on-going variations in the pattern of CVD risk factors, likely due to changes in lifestyle trends in the population over time, may yield different results when replicating this study. In addition, advances in diagnostic equipment, laboratory measurements and therapeutic services should also be considered. Therefore, the utilisation of this model may not be accurate over time. Minor revisions or adjustments to the model are suggested in future practice.

Since the general Omani population in different regions of the country are of the same ethnicity and have similar lifestyles and cultural characteristics, the present model could potentially be generalised to Omani type 2 diabetic populations in other Provinces. However, external validation studies involving samples from different provinces are required to demonstrate this supposition. The applicability of the present model in neighbouring countries in the Arabian Gulf should be considered with caution as some social and cultural differences still exist in these populations, although they share to some extent similar ethnic, lifestyle and cultural traits with Omanis. Therefore, external validation studies for the model are needed when applying the model to these populations. However, due to the strong relationship between diabetes and

multiple DM-related complications with geographical location and environmental and lifestyle characteristics, it is preferential that a specific risk assessment tool be developed for each population.[10,23,253]

7.7 Strengths and limitations of the projects

There were several strengths to this project. Using a cohort study design allowed the direct measurement of CVD incidence and the identification of multiple risk factors among the type 2 diabetic population; in addition, it provided strong evidence to estimate the likelihood of CVD over time as it was able to ensure the exposure-outcome sequence. Moreover, the study involved a sample of adequate size to study CVD incidence and patterns of CVD risk factors. As the study sample was selected from primary care settings in which all diabetics in the region are registered and managed, the sample was also representative of the target population. As such, the developed model reflects the most recent conditions concerning the type 2 diabetic population in Oman, which increases the relevance of the model to current diabetes management. Finally, this project was supported financially by the Centre of Studies and Research of the Ministry of Health in Oman and the Population and Social Health Research Program (PSHRP) of Menzies Health Institute -Queensland, emphasising its importance to public health and its unique contributions to local clinical practice. This support allowed the researcher to maximise the included sample size and quality of collected data.

In contrast, this project had also a number of limitations that are mainly related to the study design. Due to the retrospective nature of this study, information bias was the major constraint. The problems of information bias (as the data of risk factors were recorded at baseline only, no follow-ups involved) and incomplete data for some predictors, as well as recall bias related to smoking status and a family history of CVD, were major constraints. The associations between CVD and these factors might have been underestimated. However, cross-checking of different data sources may had overcome these problems to some extent. In addition, the absence of follow-up data for risk factors may have overestimated the hazard ratios of various factors since these factors are expected to be controlled over the follow-up period as a result of the

delivered treatments. On the other hand, selection bias can be a potential threat in this study as well, since patients who were not assessed for the key factors and the CVD outcome at the baseline were excluded from the beginning of the study. Also, only patients with complete data related to all key factors were included to build the final model. However, the excluded and included subjects were similar to some extent. In addition, lifestyles factors, such as dietary habits and physical inactivity, which were not addressed in this study, might have a confounding effect on the observed associations between various risk factors and CVD outcome. Future studies are recommended to include lifestyle factors and other non-traditional risk factors for CVD risk assessment. Furthermore, this study did not address the interaction effect (modification) between different factors on the CVD outcome in the multivariate analysis. Therefore, prospective studies with larger sample size can be considered in the future in order to achieve a better quality of data, to control for possible confounding factors, to study the interaction effects between various factors and to establish a more accurate temporal relationship between the risk factors and CVD outcomes. In addition, standardised data collection methods and measurements should be used to determine smoking status.

Moreover, although the model showed good performance, the validation sample was relatively small and taken from the same region. Therefore, validation studies with larger samples are needed, particularly samples external to the population used to derive the model. In addition, due to limited resources, certain factors which may affect CVD risk (including physical inactivity, dietary patterns and use of different types of anti-diabetes, anti-hypertensive and anti-lipid) were not investigated. However, the effects of these would have been to some extent accounted for by other included modifiable risk factors such as glycaemic control, HTN and lipid profile, respectively.

7.8 Conclusions and recommendations

This project included the first longitudinal study investigating CVD incidence and patterns of CVD risk factors among type 2 diabetics in Oman. Studying

CVD-related complications and risk factors is one of the primary research priorities of the Ministry of Health in Oman. The project established a useful database on CVD incidence and risk factor patterns that will help to assess the extent of the problem in Oman, and subsequently aid assessment of the required therapeutic and preventative services.

More importantly, this study produced and validated the first CVD risk assessment tool in the Arab region. The developed model showed good discrimination and acceptable calibration, indicating the validity of the model. Therefore, this model is expected to be more appropriate for CVD risk assessment among the Omani diabetics in comparison to existing global tools. The model may be used by physicians to estimate the five-year CVD risk among Omani type 2 diabetics, which is important when planning clinical management of these patients. Also, it may be utilised by health planners to estimate future projections of CVD burden among Omani diabetics. However, to further assess the generalisability of the model to a wider population, validation studies in different regions of Oman, as well in neighbouring Gulf countries, are required. Moreover, comparison studies in which the performance of the present model can be compared to existing tools, such as the WHO/ISH risk prediction charts, are recommended to evaluate the value of the present model.

The application of this model in local healthcare settings in Oman would have a great impact on public health policies and areas of future research and is crucial to improving diabetes care in Oman. In this regard, the following recommendations are addressed.

Developing and monitoring public health programs for CVD prevention among diabetics

The application of this CVD risk assessment model in local healthcare settings would aid in the development of public health policies and when planning public health preventative programs for CVD prevention among diabetics. The use of this model would enable health planners to estimate current and future CVD risk and monitor CVD burden over time. In addition, continuous

monitoring of the prevalence of CVD risk factors and incidence of CVD among the diabetic population via use of the model is crucial to assess the effects of preventative measures delivered at both the individual and population levels. Moreover, implementation of the model would enable physicians to identify and target high-risk groups for intensified preventative interventions.

Updating clinical management guidelines

Current clinical management guidelines should be revised and updated in relation to an individual patient's conditions. For example, the predicted high risk of an individual can be a useful guide when making clinical decisions regarding the intensity of preventative interventions, such as specific dietary advice, intensive physical activity and the timeliness and prescription of specific drugs to control various risk factors. In this regard, use of the model may inform preventative management planning. Subsequently, this would allow future studies to evaluate the impact of the model on patient management and trends in CVD risk among the Omani type 2 diabetic population.

Further validation and revision of the CVD model

Use of this model to assess CVD risk and monitor CVD events for existing and newly registered patients will allow researchers to further validate the model over time. However, this may periodically require that the model be revised and updated accordingly. In addition, this will allow researchers to assess the cost-effectiveness of using the model in clinical settings and to assess improvements to diabetic patient care.

Directions for future studies

Future studies may consider incorporating scientific measurements of several lifestyle factors (such as physical inactivity and dietary habits) to develop a more comprehensive CVD risk assessment model in Oman and in the broader Arabian Gulf region. In this regard, utilising bioinformatics information from the existing computerised system may be made possible to incorporate such factors in the model. Similarly, incorporating non-traditional CVD factors

excluded in the present model may also be beneficial, if including these factors would increase the accuracy of CVD prediction and clinical application of the model.

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APPENDICES

Appendix A

Permission from the publisher to include the two published articles in this thesis

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February 2, 2017

Dr. Abdul Hakeem Al-Rawahi
School of Medicine
Griffith University
Queensland, Australia

Re: Including Published Articles in PhD Thesis

Dear Dr. Abdul Hakeem,

As per your request, Oman Medical Journal has no objection to include your articles that was published in *Oman Med J* in your PhD thesis. Below are the articles permitted to be included in your thesis:

1. **Title:** Applicability of the Existing CVD Risk Assessment Tools to Type II Diabetes in Oman: A Review
   Authors: Abdul Hakeem Al-Rawahi, Patricia Lee
   Volume: 30
   Issue: 5
   Pages: 315-319
   DOI: 10.5001/omj.2015.65
   PMID: 26421110
   PMCID: PMC4576391

2. **Title:** Cardiovascular Disease Incidence and Risk Factor Patterns among Omanis with Type 2 Diabetes: A Retrospective Cohort Study
   Authors: Abdul Hakeem Al-Rawahi, Patricia Lee, Zaher A.M. Al Anqoudi, Ahmed Al Busaidi, Muna Al Rebasni, Faisal Al Mahrouqi, Ahmed M. Al Busaidi
   Pages: in press
   DOI: 10.5001/omj.2017.20

Permission was granted by:

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Appendix B

Data collection sheet

Cardiovascular Risk assessment among Omani Type 2 Diabetics

Note: included subjects must be:

- Free of CHD, Stroke and Peripheral arterial disease at baseline (2009-2010).

- All data related to risk factors (part 2) to be gathered at baseline.

- Data related to CVD outcome (part 3) to be traced from baseline to December 2015.

PART 1: Socio-demographics

-Health Institution……

-File number …… - Diabetes register No:……..

-Gender: 1-Male 2-Female

-Date of birth: ……..……/…..……../…… (Day/month/year)

PART 2: Baseline Risk Factors (i)

-Date of diagnosis of type 2 DM:……..…/…..……/…….…… (Day/month/year)

-Date of baseline check-up in 2009-2010: …..…… (Month) / 20… (Month/year)

-At baseline: WT……..… - HT……..…… (or BMI……..…..……)

-Smoking at baseline: 1-Non-smoker 2-Current smoker

3-Ex- smoker

-Patient has first degree family history of: (can tick more than one)

1- CHD 2-Stroke 3-Periphral vascular disease 4-No family H.

-HTN at baseline 1-Yes 2-No

-Average 3 BP readings at baseline SBP……...…DBP…..……..….

-Total Cholesterol level…… …LDL…..…..…HDL…….TG……..

- HbA1c……

-Confirmed Micro-macro albuminuria: 1-present 2-abcent

PART 3: End point events

-Till time of data collection (December 2015) or till death, the patient developed the following: (tick the first developed outcome & put date of diagnosis):

-Non fatal coronary heart disease 1-Yes 2-No => date if yes

……../……..…/……

- Fatal coronary heart disease 1-Yes 2-No => date if yes

……/……..…/……

-Non- fatal stroke 1-Yes 2-No => date if yes

……/……..…/…….

-Fatal stroke 1-Yes 2-No => date if yes

……/……..…/……

- PAD 1-Yes 2-No => date if yes

……/……..…/……

- Death due to non-CVD causes 1-Yes 2-No => date if yes

……/……..…/……

-Non- of above

Appendix C

Ethical approvals of the project

Sultanate of Oman
Ministry of Health
Directorate General of Health Services
AL - Dakhiliyah Governorate

سلطنة عمان
وزارة الصحة
المديرية العامة للخدمات الصحية
لمحافظة الداخلية

Saltantof Oman

AL-Dakhiliya Governorate

Regional Research&Research EthicsCommittee (RR&REC)

(Approval form)

Researcher	***Dr Abdulhakeem alrawahi / OMSB research department Dr Zaher Alanqoudi / NCDSC- DGHS ALdakhiliyah***
Title	***Epidemiological investigation of cardiovascular risk among type 2 Omani diabetics in Al-Dakhiliyah Governorate***
Approval and comment	***This study was reviewed and approved by Regional Research &Research Ethics Committee on 12/10/2014.***
Signature of Regional Research &Research Ethics Committee Chairman	***Dr.SalemHamedSaif AL-busaidi***

ص.ب : ٤٥٥ ، الرمز البريدي : ٦١١ نزوى ، هاتف : ٢٥٤١١٥٤٥ - فاكس : ٢٥٤١١٢٥٣
P.O. Box : 455. Postal Code : 611 Nizwa. Tel. : 25411545 - Fax : 25411253

GRIFFITH UNIVERSITY HUMAN RESEARCH ETHICS COMMITTEE

25-Jun-2015

Dear Dr. Al Rawahi

I write further to the additional information provided in relation to the conditional approval granted to your application for ethical clearance for your project "PR: Cardiovascular Risk Assessment Among Omani Type 2 Diabetics" (GU Ref No: PBH/01/15/HREC).

This is to confirm receipt of the remaining required information, assurances or amendments to this protocol.

Consequently, I reconfirm my earlier advice that you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.

Regards

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