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Incident Coronary Atherosclerosis, Unstable Angina, Non-ST-Segment Elevation Myocardial Infarction or ST-Segment Elevation Myocardial Infarction in Type 2 Diabetes: Is Mean Glycated Hemoglobin a Good Predictor?

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by

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Abstract

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by

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The University of Texas at Austin, 2010

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Background: Glycated hemoglobin is the indicator of long-term diabetes control and a value below 7 percent is recommended by the American Diabetes Association (ADA) to reduce cardiovascular complications. Diabetic patients have a two- to four-fold risk of cardiovascular disease and approximately two-thirds of diabetic patients die as a result of cardiovascular complications. Three large prospective randomized controlled long-term trials within the last decade reported no significant reduction in cardiovascular complications in type 2 diabetic patients by intensive glycemic control. To the author's knowledge, no known retrospective studies have examined the association between mean

serial glycated hemoglobin and coronary atherosclerosis (CA) or acute coronary syndromes (ACS).

Objective: This study was designed to determine the association between mean serial glycated hemoglobin with incident CA or ACS in type 2 diabetic patients after controlling for age, gender, hypertension, low density lipoprotein cholesterol (LDL-C), microalbuminuria, aspirin use, statin use, insulin use, tobacco use, and body mass index (BMI).

Methods: The study was a retrospective cohort database analysis using the Austin Travis County CommUnityCare^{TM} clinics' electronic medical record for the time period between October 1, 2004 and September 30, 2009. The primary outcome of the study was the incidence of CA or ACS and the primary independent variable was glycated hemoglobin (<7% vs. ≥7%). The study subjects included type 2 diabetic patients aged 30 to 80 years with at least one glycated hemoglobin value per year for a minimum of two consecutive years. Study subjects were excluded if CA or ACS occurred within six months of the index date (i.e., first glycated hemoglobin). Logistic regression analysis was used to address the study objective.

Results: Overall, 3069 subjects met the study inclusion criteria with a mean follow-up period of approximately two years. Two percent (N=62) of the subjects had incident CA or ACS. After controlling for age, gender, hypertension diagnosis, LDL-C, microalbuminuria, aspirin use, statin use, insulin use, tobacco use and BMI, there was no significant association (OR=1.026, 95% CI=0.589-1.785, p=0.9289) between mean serial glycated hemoglobin and the incident diagnosis of CA or ACS. Increasing age

(OR=1.051, 95% CI=1.025-1.077, p<0.0001), male gender (OR=1.855, 95% CI=1.105-3.115, p=0.0195) and normal weight (normal or underweight compared to obese: OR=0.122, 95% CI=0.017-0.895, p=0.0438) were significantly associated with incident CA or ACS.

Conclusions: Mean serial glycated hemoglobin (comparing ≥7% to <7%) was not significantly associated with CA or ACS over a mean follow-up period of approximately two years. Until more evidence becomes available, clinicians and diabetic patients should target glycated hemoglobin level below or close to 7 percent as recommended by the ADA soon after diagnosis while concomitantly controlling nonglycemic risk factors of cardiovascular disease (statin use, aspirin use, blood pressure control, smoking cessation and life style modification), to reduce their long-term risk of incident CA or ACS.

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CHAPTER ONE: INTRODUCTION AND LITERATURE REVIEW

1.1 CHAPTER OVERVIEW

This chapter provides a detailed review of the literature on the effect of blood glucose control in both diabetic and non-diabetic patients on the incidence of coronary heart disease. The chapter begins with a table that lists the abbreviations used (Table 1.1), followed by a brief background of type 2 diabetes. This is followed by a review of the microvascular and macrovascular complications of type 2 diabetes. Then the literature regarding the association of glycated hemoglobin with coronary heart disease in both diabetic and nondiabetic patients is presented. The chapter ends with the statement of the problem, aim of the study, and study objectives and associated hypotheses.

Table 1.1 Abbreviations and Acronyms Used in Chapters One to Four

AACE	American Association of Clinical Endocrinologists		$HbA1_C$	Glycated hemoglobin
ACCORD	Action to Control Cardiovascular Risk in Diabetes		HDL	High-density lipoprotein
ACEI	Angiotensin-converting enzyme inhibitor		HDL-C	High-density lipoprotein cholesterol
ACS	Acute coronary syndromes		IHD	Ischemic heart disease
ADA	American Diabetes Association		IFG	Impaired fasting glucose
ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation		IMT	Intima-media thickness
AMI	Acute myocardial infarction		LDL	Low-density lipoprotein
ARB	Angiotensin receptor blocker		LDL-C	Low-density lipoprotein cholesterol
BMI	Body mass index		MI	Myocardial infarction
CA	Coronary atherosclerosis		NSTEMI	Non-ST-segment elevation myocardial infarction
CCA	Common carotid artery		NHIS	National Health Interview Survey
CDC	Center for Disease Control and Prevention		PVD	Peripheral vascular disease
CHD	Coronary heart disease		STEMI	ST-segment elevation myocardial infarction
CIMT	Carotid intima media thickness		T2DM	Type 2 diabetes mellitus
CRP	C-reactive protein		TG	Triglycerides
CVD	Cardiovascular disease		UA	Unstable angina
DCCT	Diabetes Control and Complications Trial		UKPDS	United Kingdom Prospective Diabetes Study
ESRD	End-stage renal disease		US	United States
FFA	Free fatty acid		VADT	Veterans Affairs Diabetes Trial

1.2 BACKGROUND OF TYPE 2 DIABETES

1.2.1 Epidemiology and Classification

Type 2 diabetes mellitus (T2DM), a disorder of carbohydrate metabolism, is a chronic disease associated with poor cardiovascular outcomes. Approximately 90 percent of diabetes patients have T2DM and the remaining 10 percent have type 1 diabetes, also known as insulin dependent diabetes.[1] Diabetes prevalence is increasing in the United States (US). In 2007, it was estimated that 23.6 million Americans or 7.8 percent of the US population had diabetes. In 2008, the Centers for Disease Control and Prevention (CDC) released new statistics stating that over 24 million Americans had diabetes.[2] Although prevalence of diabetes is approximately equal for males and females, it differs across racial/ethnic categories. The highest rate of diabetes is among Native Americans (16.5%) and Alaskan Natives (16.5%), whereas the lowest rates are among Asian Americans (7.5%) and Whites (6.6%). The rate of diabetes in Blacks is 11.8 percent and the rate among Hispanics is 10.4 percent.

The leading cause of morbidity and mortality among T2DM or type 1 diabetic patients is cardiovascular disease (CVD), which consists of coronary heart disease (CHD), stroke, peripheral vascular disease (PVD), hypertension and congestive heart failure.[3] Coronary heart disease consists of acute coronary syndromes (ACS) which includes unstable angina (UA) pectoris, acute myocardial infarction (AMI), and small vessel coronary artery disease.[4-5] In 2004, approximately 68 percent of deaths in

diabetic patients were due to CVD, with CHD as the leading cause.[6] Haffner et al. showed that the risk of MI in diabetic patients is equivalent to non-diabetic patients with previous history of MI [7] and long-term morbidity and mortality after an MI is worse in diabetic patients compared with non-diabetics.[8] Diabetes is therefore considered a coronary artery disease risk equivalent, with a 10-year cardiovascular event risk greater than 20 percent.[9] Other risk factors for CVD in diabetic patients include age, hypertension, family history of early CVD, dyslipidemia, smoking, microalbuminuria, and obesity.[10-11] Microvascular complications in diabetic patients are also predictors of CVD.[12] According to the National Health Interview Survey (NHIS), approximately six million Americans 35 years and older with diabetes were affected with CVD. Of those, 65 percent reported having CHD.[13] Therefore, aggressive management of diabetes is needed to reduce the risk of CHD.

Glycated hemoglobin ($HbA1_C$), an estimate of a patient's average blood glucose level over the previous ten to twelve weeks, is the biological marker of diabetes control. An $HbA1_C$ value below seven percent is recommended by the American Diabetes Association (ADA) to reduce microvascular and macrovascular complications of diabetes.[14] However, the association between $HbA1_C$ and incidence of ACS has not been consistent in both clinical trials and prospective epidemiological studies of diabetic and non-diabetic patients.[15] No known retrospective cohort database studies in the literature have examined the association between mean serial values of $HbA1_C$ prior to first diagnosis of coronary atherosclerosis (CA) or ACS and incidence of CA or ACS. The retrospective study design (compared to clinical trials or prospective cohorts) has an

advantage of assessing "real-world" (effectiveness) outcomes. The overall purpose of this study is to determine whether incident CA or ACS is associated with mean $HbA1_C$ in T2DM patients.

1.2.2 Complications of Type 2 Diabetes

Long-term morbidities of poorly controlled T2DM are microvascular and macrovascular complications.[16] Microvascular complications include nephropathy, neuropathy and retinopathy; and macrovascular complications involve the vasculature of the cardiovascular system. Coronary heart disease, PVD, increased carotid intima-media thickness (IMT) and stroke are the main macrovascular complications of diabetes. Diabetic patients are living longer and therefore have a high probability of developing diabetes complications in their lifetimes. However, these vascular complications can be delayed or prevented by glucose control, in addition to the following interventions on modifiable risk factors; blood pressure control, regular physical activity, healthy diet, lipid control, smoking cessation and medications. These include angiotensin-converting enzyme inhibitor (ACEI) therapy, statin therapy, and aspirin therapy when indicated.[16] After a mean follow-up of 7.8 years, the Steno-2 trial demonstrated that a multifactoral intervention aimed at the modifiable risk factors in type 2 diabetic patients with concomitant microalbuminuria decreased the risk of both cardiovascular and microvascular events by 50 percent.[17]

1.2.2.1 Microvascular Complications

As mentioned above, microvascular complications include nephropathy, neuropathy and retinopathy. In the US, diabetic nephropathy is the leading cause of end-stage renal disease (ESRD), which requires dialysis or transplantation,[18] with diabetic ESRD prevalence increasing from 24.4 per million population in 1980 to 634.8 per million population in 2007.[15] Diabetic nephropathy increases morbidity and when diabetic nephropathy progresses to ESRD, it significantly increases morbidity and mortality. Over 20 to 40 percent of diabetic patients develop ESRD after 15 to 20 years of diabetes onset.[18] Data from pooled studies have shown that diabetic nephropathy is an independent risk factor for developing CVD among diabetic patients [19] irrespective of age, sex, blood pressure and lipid levels.[20] An early marker for diabetic nephropathy is microalbuminuria (microalbumin/creatinine ratio). Microalbuminuria is defined as urinary excretion of albumin of 20-200 micrograms per minute or proteinuria greater than 500 mg in a 24-hour urine collection.[10] In addition, a spot urine test for microalbuminuria that utilizes a random (nontimed) sample is available. This test is frequently employed to screen for nephropathy in the ambulatory setting because of its convenience. A ratio of 30-300 mg/g from the spot test is diagnostic of microalbuminuria (normoalbuminuria is a ratio < 30 mg/g).[18] Hypertension and uncontrolled diabetes are associated with a decline in renal function [18]. With many diabetic patients having concomitant hypertension, there is also an additive risk of nephropathy. New onset diabetic nephropathy or the progression to ESRD can be delayed with tight control of blood glucose and blood pressure. Blood pressure medications (angiotensin converting

enzyme [ACE] inhibitors and angiotensin receptor blockers [ARBs]) have been shown to be renoprotective independent of their blood pressure lowering effect. In diabetic patients with microalbuminuria, ACE inhibitors and ARBs have been shown to decrease the progression from microalbuminuria to macroalbuminuria by approximately 60-70 percent.[12]

Diabetic neuropathy is a complication that affects the nerves in the nervous system. A wide range of prevalence rates (5-100%) of diabetic neuropathy have been reported, depending on the diagnostic criteria.[21] Most of the hospitalizations from diabetes complications are due to neuropathy because it accounts for 50-70 percent of lower limb amputations. Diabetic neuropathy damages peripheral, motor, sensory and autonomic nerves; hence, it is a polyneuropathic condition.[10] The most common neuropathy in diabetes patients is the peripheral neuropathy that presents initially as pain and tingling in the toes and worsens at night.[22] This then progresses to loss of sensation in the feet and frequent foot ulcers, which lead to amputations. Regular screening for diabetic neuropathy is essential for early detection. Inexpensive and noninvasive devices for assessing nerve sensation in diabetic patients are available and screening methods include vibration, thermal energy and light touch sensation.[10] The gold standard for diagnosing diabetic neuropathy is clinical electrophysiology[22], but most primary care physicians use the light touch sensation or the vibration methods in clinical practice. In addition, several pharmacologic options are available for the treatment of neuropathic pain. These include antidepressants (e.g., amitriptyline and

duloxetine), anticonvulsants (e.g., phenytoin, carbamazepine, gabapentin, pregabalin), and analgesics (e.g., tramadol and opioids).[21]

In the US, diabetic retinopathy is the leading cause of blindness among individuals between the ages of 20-74 years. Retinopathy is sometimes present at the time of diabetes diagnosis [23] and it is estimated that over 60 percent of T2DM patients will develop some level of retinopathy after two decades of diabetes onset.[23] With diabetic retinopathy, damage to blood vessels in the retina of the eye occurs as a result of persistent hyperglycemia. The early stages of diabetic retinopathy that do not affect vision are treatable and with subsequent tight blood glucose control, the progression to blindness can be delayed.[23] The ADA recommends referral of a diabetic patient to an ophthalmologist for a dilated eye examination immediately after diagnosis and then annually. Annual referral to an ophthalmologist is recommended to ensure that new onset retinopathy can be detected early for treatment, and that patients with diabetic retinopathy receive the appropriate care**.**

1.2.2.2 Macrovascular Complications

The common macrovascular complications of diabetes are collectively termed CVD (i.e., CHD, PVD, increased CIMT and stroke). They are the leading cause of morbidity and mortality among diabetic patients. Other risk factors for CVD in addition to diabetes are dyslipidemia, hypertension and smoking. These coronary risk factors damage the inner most layer of the arterial vessel (i.e., endothelium) resulting in endothelial dysfunction which plays an important role in initiating the atherosclerotic process.[24] A functional vascular endothelium resists clot formation, helps form

collateral circulation and regulates blood flow via production of nitric oxide, a vasodilator which primarily mediates vascular reactivity.[25]

Atherosclerosis is a gradual process that occurs throughout a person's lifetime and targets the large- and medium-sized arterial walls throughout the body, eventually manifesting itself as an ischemic event such as MI or stroke.[26] Persistent high blood glucose levels over time in diabetic patients result in glucose binding to arterial wall proteins, which forms advanced glycation end products. These products accumulate over time and progressively lead to increased arterial wall stiffness and structural changes that compromise wall function, accelerate atherosclerosis and increase the risk of arterial thrombotic complications.[25, 27-30] Other proposed mechanisms by which diabetes impair endothelial function are oxidation of low-density lipoprotein (LDL), hyperinsulinemia[31], oxidative stress[32] and increased concentrations of free fatty acids (FFA).[25]

Low-density lipoprotein is not the only cholesterol implicated as a risk factor for atherosclerotic ischemic heart disease (IHD). The Copenhagen Male Study demonstrated that diabetic dyslipidemia (high LDL-C, low HDL-C, and high TG) was a more powerful predictor of atherosclerotic IHD than isolated increased LDL-C levels.[33] Also, hyperinsulinemia depicted by high fasting plasma insulin concentrations is usually associated with high TG and low HDL-C. Results of prospective and observational studies depict hyperinsulinemia as an independent predictor of ischemic heart disease.[31] Furthermore, the effect of increased oxidative stress (a relative increase in oxygen free radicals) on endothelial dysfunction in atherosclerosis has been demonstrated

in a study that compared vascular superoxide production in diabetic and nondiabetic patients. Guzik and colleagues reported that in diabetic patients, there is increased production by blood vessel endothelium of superoxide (surrogate for oxidative stress), resulting in decreased nitric oxide which scavenges the superoxide, [32] leading to endothelial dysfunction. Finally, Steinberg and colleagues concluded from a study evaluating the effect of plasma FFA levels on endothelium-dependent vasodilation that elevated circulating FFA levels cause endothelial dysfunction hypothetically via an effect on the nitric oxide system.[34]

The consequences of a dysfunctional endothelium include decreased release of chemicals like nitric oxide that reduce the risk of arterial thrombosis and increased release of prothrombotic agents including endothelin-1 and vascular and intercellular adhesion molecules.[24] In addition, inflammatory monocytes differentiate into activated macrophages that convert LDL-C embedded in the arterial wall into foam cells called plaques. Thus, heterogenous plaques are rich in lipids, connective tissue elements or debris.[35] Activated macrophages release inflammatory cytokines that fuel the plaque formation process. The macrophages also play a role in activating enzymes that digest the extracellular matrix around the embedded plaque leading to plaque instability, making it vulnerable to rupturing and causing an ischemic event. It is important to note that over 99 percent of cases of plaque rupturing result in clinically silent events, [24] and in the case of a symptomatic event, there are multiple plaque ruptures which are different from the culprit plaque. Inflammation is a very important determinant of vulnerable plaques and it correlates with increased density and activity of macrophages at the site of the

plaque as well as levels of C-reactive protein (CRP). The degree of thrombus formation determines whether the rupture of plaque will result in a symptomatic ischemic event and plaque rupture results in acute partial or total vascular blockage.[12] Two types of thrombi can be formed: a platelet rich one (white clot) which only partially occludes the artery; or a fibrin-rich clot (red clot) that usually forms total occlusion of the arterial lumen. These fibrin rich clots are larger because they are formed as a result of the activation of the coagulation cascade.[24]

Carotid intima media thickness (CIMT) and aorta measured ultrasound are methods for assessment of the generalized atherosclerosis including CA.[10, 36] CIMT testing is a noninvasive process that directly measures atherosclerotic changes in the carotid artery and thickness in the intima layer of the carotid artery has been correlated with CA. CIMT testing has been utilized in clinical trials that have evaluated the effect of pharmacotherapeutic agents on the diagnosis and progression of atherosclerosis. On the other hand, intravascular ultrasound can be used to directly examine the coronary arteries for atherosclerosis, but CIMT measurements are easier to perform.[37]

Peripheral vascular disease is generally characterized by the absence of femoral pulses as a result of the partial or complete occlusion of the arteries supplying the lower periphery with blood. Occlusion of arteries in the periphery is secondary to arthrosclerosis. Symptoms include intermittent claudication, numbness and weakness of lower extremities, and painful ulcers. The risk of PVD is proportional to the magnitude and duration of hyperglycemia and diabetic patients have two-to four-fold higher rates of PVD than the normal population.[38] Other risk factors for PVD are dyslipidemia,

smoking, obesity, hypertension, chronic renal failure and physical inactivity.

Stroke occurs when there is disruption of blood flow to a part of the brain due to atherosclerotic narrowing of small arteries within the brain or the large arteries leading to the brain. Adverse impact of diabetes on cerebrovascular arterial circulation increases the risk of stroke by 150 to 400 percent in diabetic patients, with the risk more profound in patients under 55 years.[38]

With almost all types of CHD, CA causes the narrowing of the arteries that supply the heart muscle with blood. The atherosclerotic thickening of arterial wall in CHD occurs in the endothelium of the artery and atherosclerotic plaque(s) progressively cause the narrowing of the vessel lumen.[36] Acute myocardial ischemic states, as a result of CA, result in CHD.[24] The universal symptom of a suspected CHD event is chest pain stemming from myocardial ischemia. In both unstable angina (UA) and (non-ST-segment myocardial infarction (NSTEMI), there is an imbalance of oxygenated blood demand and supply to a heart muscle as a result of partial occlusion of blood flow from atherosclerosis. The decrease in oxygenated blood supply manifests in chest pain, with NSTEMI symptoms being more severe (i.e., results in the release into blood of either cardiac-specific troponins or muscle and brain fraction of creatine kinase) than that of UA.[4] In most cases of ST-segment myocardial infarction (STEMI), the rupture of an atherosclerotic plaque leads to an immune response that forms a thrombus around the plaque. The plaque together with the thrombus totally occludes blood flow through the coronary artery to a heart muscle, leading to chest pain.[35] In the US, approximately two-thirds of patients with MI have NSTEMI and the remaining one-third have STEMI;

both of which are differentiated by an electrocardiogram.

1.3 GLYCATED HEMOGLOBIN AND CARDIOVASCULAR OUTCOMES

1.3.1 Glycated Hemoglobin

Glycated hemoglobin is the accepted surrogate marker of long-term blood glucose control in diabetes patients. Both the ADA and the American Association of Clinical Endocrinologists (AACE) recommend utilization of $HbA1_C$ to assess long-term diabetes control, but with slightly different goals (7% vs. 6.5% respectively).[39-40] $HbA1_C$ is an estimate of average blood glucose over the preceding ten to twelve weeks and is expressed as the percent of glycated hemoglobin in blood.[41] Standardized $HbA1_C$ assays are used, hence $HbA1_C$ results are interpreted consistently worldwide.[14] However, individuals with sickle cell, hemolytic anemia, chronic malaria, major blood loss or frequent blood transfusion may have spurious $HbA1_C$ results as a result of increase red blood cell turnover.[42] Normal $HbA1_C$ in a nondiabetic patient is less than six percent.[39] Per the 2010 ADA Standards of Diabetes Care, $HbA1_C$ greater than or equal to six and half percent measured on two separate occasions is diagnostic of diabetes.[14] Use of $HbA1_C$ for diagnosis of diabetes was recommended by the International Expert Committee Report on the Role of the $A1_C$ Assay in the Diagnosis of Diabetes in 2009 [42] and the ADA added the recommendation to its 2010

guidelines.[14] The ADA recommends target $HbA1_C$ less than seven percent in diabetic patients to prevent microvascular and macrovascular complications of diabetes and this is based on findings from epidemiological studies. This target $HbA1_C$ corresponds to an average blood glucose of 154 mg/dL in the previous ten to twelve weeks.[41]

1.3.2 Glycated Hemoglobin or Blood Glucose and Cardiovascular Outcomes

1.3.2.1 Non-Diabetic Patients

A German study that analyzed the relationship between fasting plasma glucose, CIMT and some atherosclerosis risk factors in 300 nondiabetic patients no longer had a significant correlation between fasting blood glucose and IMT after adjusting for age and sex.[43] However, glycated hemoglobin has been associated with the incidence of CHD in nondiabetic patients. A recent large Australian cohort study, by Adam et al., of nondiabetic patients showed a positive association between HbA_{1C} >5.3 percent compared with patients with $HbA1_C$ ≤5 percent and incidence of CHD in both men and women, with a stronger association in women ($HbA1_C$ 5.4-5.6% [odds ratio 2.5, 95% CI 1.4-4.6] and $HbA1_C$ ≥5.7% [odds ratio 1.9, 95% CI 1.1-3.4]). This association persisted after adjusting for impaired fasting glucose (IFG), hypertension, hypercholesterolemia, body mass index (BMI), waist circumference, and tobacco smoking.[44] Similarly, Hoogwerf et al., demonstrated, in a cross-sectional study, that glucose was independently

associated with incidence of CHD in nondiabetic patients. The results of the study showed that across the range of recommended fasting blood glucose levels (100-125 mg/dL) divided into five quintiles (<79, 80-86, 87-92, 93-99, 100-125 mg/dL), there was a significant increase in CHD prevalence ($p < 0.001$) with increasing range of fasting blood glucose levels.[45]

1.3.2.2 Diabetic Patients

Most of the morbidity and mortality for diabetes are a result of complications of atherosclerosis which manifests clinically in three vascular beds namely coronary arteries, peripheral arteries and extracranial carotid arteries.[38] Apart from the fact that diabetes patients with no history of CHD have the same risk for future MI as do nondiabetic patients with history of CHD, diabetes also negates the female decreased risk for death from CHD.[25] Larsen and colleagues reported a strong association between IMT of the CCA, a validated surrogate marker of preclinical CA, and long-term $HbA1_C$ (mean=8.2%, range=6.6-11.3%) in asymptomatic females with type 1 diabetes mellitus ($r^2=0.77$, $p<0.0001$), but not males.[37] The mean $HbA1_C$, which was the predictor variable, was calculated from the first $HbA1_C$ each year and was measured prospectively for 18 years. The authors could not explain their finding that long-term hyperglycemia was a stronger risk factor for the development of atherosclerosis in women than in men. In addition, Roger and colleagues conducted an anatomical study of atherosclerosis using an autopsied population in the Olmstead county of MN to examine the association between diabetes and CA.[46] Two measures (global coronary score and high grade stenoses) were employed to measure the prevalence of atherosclerosis. There was a

higher prevalence of CA among diabetic individuals than among nondiabetic individuals (prevalence ratio, PR=1.5, 95% CI 1.3-1.7, p<0.001). Another important finding of this study was that approximately 75 percent of diabetic individuals without CAD had CA, which was similar to that observed in nondiabetic individuals with CAD.

The authors of the Diabetes Control and Complications Trial (DCCT) reported that tight control of blood glucose assessed by the reduction in $HbA1_C$ reduces the risk of long-term microvascular complications in type 1 diabetic patients,[47] but did not demonstrate delay in macrovascular complications with tight glucose control. Similarly, after a median follow up of ten years (interquartile range 7.7-12.4 years), the authors of the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that tight glucose control in T2DM patients using sulfonylurea or insulin to maintain a median $HbA1_C$ of seven percent versus conventional treatment of diet significantly reduced microvascular complications risk by 25 percent (p=0.0099), but not myocardial infarction (16% reduction in risk, p=0.052).[48] However, after a mean follow-up of 17 years of the DCCT sample, the researchers reported that with tight glucose control, a 50 percent reduction in cardiovascular complications occurred.[49] A major limitation of both the DCCT and UKPDS is the predominance of Caucasians, 96 and 80 percent respectively.

In a review by Goff et al., the authors concluded that the relationship between lowering $HbA1_C$ and the incidence of CA or ACS (including CHD) in diabetic patients has not been consistent among studies.[50] Prospective epidemiological studies demonstrated the incidence of CVD was strongly associated with the level of hyperglycemia as measured by glycated hemoglobin.[51] A meta-analysis of 13

observational studies (N= 9,123) of diabetes patients (n=7,435 T2DM patients), after adjustment for risk factors, resulted in a significant increased risk of 18 percent (RR 1.18 95% CI 1.10-1.26) for CVD (CHD + stroke) for each percentage increase in HbA_{1C}.[52]

The Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE), and Veterans Affairs Diabetes Trial (VADT) are well designed studies within the last five years that reported no significant reduction in CVD (including CHD) with intensive control of blood sugar.[53]

ACCORD was a prospective randomized study of 10,251 T2DM patients with either prior CVD (35%) or additional risk factors for CVD.[54] Patients were on average 62.2±6.8 years, and had a median $HbA1_C$ of 8.1 percent at baseline. Patients were assigned to either intensive or standard therapy of glucose control. The intensive therapy targeted $HbA_{1C} < 6$ percent and standard therapy targeted HbA_{1C} of 7 to 7.9 percent. The primary outcome was a composite of nonfatal MI, nonfatal stroke, or death from CVD. Median $HbA1_C$ levels were 6.4 percent and 7.5 percent at one year in the intensive therapy and standard therapy groups, respectively, and were stable for the duration of follow-up. Intensive therapy was discontinued after a mean of three and one-half years due to increased mortality. There were 257 deaths reported in the intensive therapy group compared to 203 in the standard therapy group (HR 1.22; 95% CI 1.01-1.46; p=0.004). Incidence of major CVD (i.e., the first occurrence of nonfatal MI or nonfatal stroke or death from cardiovascular causes) did not differ significantly between the intensive and standard therapy groups (p=0.16). The increase in mortality in the

intensive therapy group was associated with the degree and pace of glucose lowering, which might have resulted in hypoglycemic episodes that led to patient deaths.

ADVANCE was a prospective randomized controlled study of 11,140 T2DM patients who had either a history of major macrovascular or microvascular disease or one other risk factor for vascular disease. Patients were randomized to either a standard glucose control (target $HbA1_C$ defined by local guidelines [n=5,569]) or intensive glucose control (target $HbA1_C \leq 6.5\%$ [n=5,571]) groups and were followed for a median duration of five years.[49] Patients were on average 66.0±6.0 years and with average duration of diabetes (8.0±6.4 years). The mean ± SD (median) $HbA1_C$ was 7.5 ± 1.6 (7.2) percent at baseline. At enrollment, 7.2 percent and 32.3 percent of patients had a history of macrovascular complications. The primary endpoints were composites of major cardiovascular events (deaths from cardiovascular causes, nonfatal MI, or nonfatal stroke) and major microvascular events (nephropathy or retinopathy). Mean $HbA1_C$ was 6.5 percent in the intensive control group and 7.3 percent in the standard control group after a median follow-up of five years. The HR in the intensive glucose control group compared to the standard glucose control group for combined major macrovascular and microvascular events was 0.90; 95% CI, 0.82 to 0.98; p=0.01. However, for major macrovascular events alone, there were no significant differences between the two groups (HR with intensive glucose control 0.94; 95% CI 0.84 to 1.06; p=0.32). The significant effect of intensive glucose control on combined major macrovascular and microvascular events, but not macrovascular events alone was attributed to the 21 percent relative risk reduction in nephropathy (microvascular event), hence intensive glucose control resulted

in a significant reduction in the incidence of major microvascular events in the ADVANCE trial. Deaths from cardiovascular causes were similar between the two groups, a contrast with the ACCORD findings. The similarity of macrovascular events and deaths between the two groups may be explained by the cumulative damage from high $HbA1_C$ values since diabetes diagnosis; therefore, the tight glucose control during the trial had little effect on macrovascular and mortality outcomes. The ADVANCE trial has limited generalizeability to the US population because approximately 83 percent of the study participants were from Asia and Europe and with only four percent from North America.

VADT was an open-label study that enrolled 1,791 military veterans with poorly controlled type 2 diabetes for a median follow up of 78 months.[53] Patients were on average 60.4 ± 9 years, had diabetes for 11.5 ± 7.5 years, and average $HbA1_C$ of 9.4 ± 2.0 percent. Patients were randomly assigned to receive either intensive (n=892) or standard glucose control (n=899). The primary outcome was time from randomization to first occurrence of a major cardiovascular event (i.e., MI, stroke, death from cardiovascular causes, congestive heart failure, surgery for vascular disease, inoperable coronary disease, and amputation for ischemic gangrene). After follow up, the median $HbA1_C$ values in the intensive glucose control and standard glucose control groups were 6.9 percent and 8.4 percent, respectively. The hazard ratio in the intensive-therapy group for the time to first occurrence of first cardiovascular event was not significant (HR, 0.88; 95% [CI], 0.74 to 1.05; p=0.14). Duckworth and colleagues concluded from the VADT study that intensive blood glucose control in poorly controlled type 2 diabetes did not

significantly decrease the rates of major cardiovascular events. A major limitation of the VADT study was that the study population was predominantly male (97%).

Selvin et al conducted a case-cohort study using data from the ARIC (Atherosclerosis Risk In Communities) study. The ARIC study was a four community US-based cohort study of 15,792 individuals who were between the ages of 45 to 64 years at baseline. Cardiovascular disease risk factor information was collected from the ARIC study subjects at baseline and study participants were followed for eight years. In the prospective case-cohort study by Selvin et al, 1,321 adults without diabetes and 1,626 adults with diabetes were evaluated in two independent groups (diabetic and nondiabetic) using the baseline $HbA1_C$ as the main predictor of CVD risk. Four quintiles of $HbA1_C$ were created for the diabetic (<5.2%, 5.2 to <5.7%, 5.7 to <6.5%, 6.5 to <8.2% and ≥8.2%) and nondiabetic (<4.5%, 4.5 to <4.8%, 4.8 to <4.9%, 4.9 to <5.2% and ≥5.2%) cohorts respectively. After adjusting for covariates (i.e., age, sex, smoking, BMI, waist-hip ratio, education, physical activity, systolic and diastolic blood pressure, hypertension medication, lipids), the relative risk (HR and 95% CI from Cox proportional hazards model) of CHD were significant for two quintiles and were 2.04 (1.30-3.19) for the $HbA1_C$ category 6.5 to <8.2% and 2.37 (95% CI 1.50-3.72, p=0.01) for the highest quintile of $HbA1_C$ level compared with the lowest quintile. In the nondiabetic cohort, the adjusted RR of CHD was not significant for each of the $HbA1_C$ quintiles.[55]

1.3.2.3 Mean Serial Glycated Hemoglobin and Cardiovascular Outcomes

Little is known about the association between mean serial $HbA1_C$ values preceding an atherosclerotic coronary event and the occurrence of the coronary event. Studies that evaluated the effects of glycemic control in T2DM patients on CVD provided inconsistent evidence even though pooled analysis of prospective studies have shown continuous associations of $HbA1_C$ levels with the risk of major vascular events.[52] Larsen and colleagues [37] observed a significant correlation between 18-year average $HbA1_C$ and common carotid artery (CCA) IMT (an indicator of CA) [56]in type 1 diabetic females. Also, several studies of T2DM patients have evaluated the effect of reduction in $HbA1_C$ (i.e., treating to a target $HbA1_C$) on the incidence of cardiovascular events. A meta-analysis of ten studies of T2DM patients showed an 18 percent increase in the risk of CVD for each one percent increase in $HbA1_C$. Also, a pooled analysis of six studies in the same meta-analysis found a significant increase in the risk of CHD by 13 percent for each one percent increase in $HbA1_C$.[52] Furthermore, other prospective epidemiologic studies have shown that the benefit of blood glucose reduction in preventing CVD is demonstrated even in patients with baseline $HbA1_C$ values below six and half percent.[50][50]

A mean serial $HbA1_C$ is being used as a predictor variable in this study instead of baseline $HbA1_C$ or median $HbA1_C$ in order to account for the contribution of individual $HbA1_C$'s damage on the vascular system over the study period while taking into account when each HbA1C was measured. In other words, the predictor variable will give equal weight to each patient's $HbA1_C$ value recorded during the follow-up period. The

DCCT/EDIC (Epidemiology of Diabetes Interventions and Complications) Study Research Group followed the DCCT cohorts in an observational study after the DCCT trail ended. The researchers reported that, after a mean follow-up of 17 years of the DCCT data, the decrease in $HbA1_C$ values in the intensive arm of the DCCT study significantly reduced the risk of CVD.[57] This implies that the effect/benefit on diabetes vascular complications of a specific $HbA1_C$ achieved after an intervention may persist over a longer period of time. Holman et al. confirmed the sustained benefit in reducing the risk of diabetic complications for up to ten years post the UKPDS study.[58]. The researchers found that even though the lower glycemic goal achieved in the intensive group of UKPDS eroded within one year (compared to conventional therapy) post trial follow-up, the significant reduction of diabetes complications achieved during the ten-year median follow-up of UKPDS persisted after ten years in 3277 subjects of the original UKPDS cohort and even found a significant relative risk reduction of MI (15%, p=0.01) which was not found at the end of the original UKPDS study.

Retrospective cohort database studies of T2DM patients have not tested whether the mean serial $HbA1_C$ values preceding the diagnosis of an atherosclerotic CHD can predict the risk of occurrence of the atherosclerotic CHD. Retrospective analyses have the advantage of capturing "real-world" longitudinal data and will probably provide a more practical and generalizeable evidence regarding the relationship between incident CA or ACS and mean serial $HbA1_C$.

1.3.3 Summary of Evidence

Studies have shown increased risk of atherosclerosis in diabetes patients compared to the general population. The landmark prospective clinical diabetes studies, DCCT and UKPDS, showed that aggressive management of blood glucose reduces the incidence of microvascular complications of diabetes [47-48], but per recent well-designed large prospective studies (i.e., ACCORD, ADVANCE, VADT), the effect on cardiovascular disease (macrovascular complication) was not significant.[49, 53-54] However, it is known that the risk of a cardiovascular event in a diabetic patient is similar to that of a nondiabetic patient with a prior history of a cardiovascular event.[7] In addition, for nondiabetic persons with normal $HbA1_C$ (i.e., < 7%) and FBS, it has been shown that persons with $HbA1_C$ and FBS in the upper limit of normal range have a higher risk of cardiovascular event than persons with values in the lower limit of normal range.[44-45] Furthermore, an epidemiological study and reviews from pooled studies have shown substantial increase in the risk of cardiovascular events in T2DM patients with increasing $HbA1_C$ levels.[52, 55] Finally, the mean or median follow-up of the randomized prospective studies of diabetes control and cardiovascular outcomes ranged from three and one-half to ten years [47-49, 53-54], long enough to detect significant reductions in macrovascular complications from aggressive management of diabetes in each study respectively.

1.4 STATEMENT OF THE PROBLEM, OBJECTIVES AND HYPOTHESES

1.4.1 Statement of the Problem

Additional research is needed to provide more evidence on whether mean serial $HbA1_C$ values are useful predictors of incident CA or ACS (i.e., UA, NSTEMI, STEMI) in diabetic patients. To the author's knowledge, no retrospective database cohort analysis has used mean serial $HbA1_C$ as the predictor variable for incident CA or ACS.

1.4.2 Aim of the Study

The aim of this study is to determine the significance of mean serial $HbA1_C$ in predicting the diagnosis of incident CA or ACS in type 2 diabetic patients by comparing a cohort with mean serial $HbA1_C$ <7 percent to a cohort with mean serial $HbA1_C$ ≥7 percent.

1.4.3 Study Significance

Results of this study may add to the body of literature regarding whether clinicians should target $HbA1_C$ levels close to the ADA goal of <7 percent at all times in all or focus on specific diabetes patients soon after diagnosis. Achieving this target in patients with difficult-to-control diabetes soon after diagnosis may reduce their risk of incident CA or ACS.

1.4.3.1 What Differentiates Study From Previous Studies

This study had several unique features that distinguish it from other studies presented in this chapter. First, the predominant population in the study was Hispanics with about an equal representation of African Americans (Blacks) and Whites. Hispanics and Blacks are two minority ethnicities/races usually not adequately represented in non-ethnic based clinical studies. However, in the US, Hispanics and Blacks represent approximately 22 percent of diabetic patients compared to approximately 14 percent White and 14 percent Asians.[2] Second, an outcome of this study is atherosclerosis which is a precursor to cardiovascular disease. Atherosclerosis has not been studied as an outcome in most well-designed prospective studies probably because of its variability in time to becoming symptomatic. This study's inclusion of atherosclerosis as an outcome may further support the ADA guidelines. These guidelines recommend aggressive management of diabetes to prevent atherosclerosis and subsequent CHD because the prevalence of aggressive atherosclerosis among diabetic patients without established clinical CHD is similar to the prevalence among nondiabetic subjects with clinical CHD. Lastly, a retrospective cohort analysis using data obtained from routine patient follow-up is a more "real-world" approach (i.e., compared to treat-to-target in prospective studies) to follow the progression of diabetic patients (in terms of comprehensive management of diabetes and cardiovascular risk factors) prior to the outcome of interest.

1.4.4 Study Objectives and Associated Hypotheses

The objectives and hypothesis of this study were:

Objective One: To describe the demographic and clinical characteristics of T2DM patients with CA or ACS (i.e., UA, NSTEMI, and STEMI).

Objective Two: To examine the relationship between incident diagnosis of CA or ACS and $HbA1_C$.

H_{02A1}: There is no statistically significant difference in incident diagnoses of CA or ACS between the $HbA1_C$ <7 percent and $HbA1_C \geq 7$ percent groups.

Objective Three: To determine the associations of incident CA or ACS with $HbA1_C$ in T2DM patients after controlling for age, gender, hypertension, LDL-C, microalbuminuria, aspirin use, statin use, insulin use, tobacco use, and BMI.

H_{03A1}: There is no statistically significant difference in incident diagnosis of CA or ACS between the $HbA1_C$ <7 percent and $HbA1_C \geq 7$ percent groups while controlling for covariates.

H_{03B1}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *age*, while controlling for other covariates.

H_{03B2}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *gender*, while controlling for other covariates.

H_{03B3}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *hypertension diagnosis*, while controlling for other covariates.

H_{03B4}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *LDL-C*, while controlling for other covariates.

H_{03B5}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *microalbuminuria*, while controlling for other covariates.

H_{03B6}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *aspirin use*, while controlling for other covariates.

H_{03B7}: There is no statistically significant relationship between incident diagnosis of CA or ACS *statin use*, while controlling for other covariates.

H_{03B8}: There is no statistically significant relationship between diagnosis of CA or ACS and *insulin use*, while controlling for other covariates.

H_{03B9}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *tobacco use*, while controlling for other covariates.

H_{03B10}: There is no statistically significant relationship between incident diagnosis of CA or ACS and *BMI*, while controlling for other covariates.

CHAPTER TWO: METHODS

2.1 CHAPTER OVERVIEW

The methodology used is described in the following order: study design, data source; study population and inclusion criteria; study cohorts, index date, and timeframe; study outcomes; study variables; and statistical analysis.

2.2 INSTITUTIONAL REVIEW BOARD APPROVAL

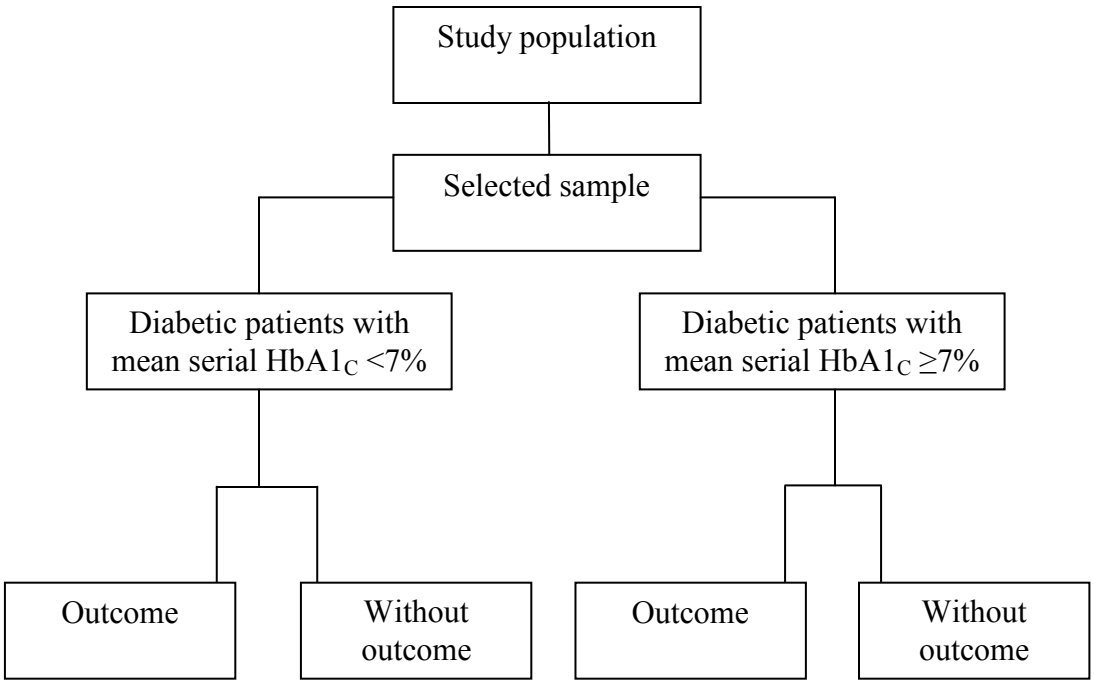
The study was approved by the Institutional Review Board (IRB) of The University of Texas at Austin (IRB protocol number: 2009-07-0013) and permission was obtained from CommUnityCare™ in Travis County, Texas to utilize patient data. A waiver of informed consent was obtained since the study will not impact the medical care of the patients involved.

2.3 STUDY DESIGN

This study is a retrospective database cohort analysis of type 2 diabetic patients to examine the association between incident CA or ACS and $HbA1_C$. Patients were stratified into two groups based on their HbA1c levels ($HbA1_C$ <7%, and HbA1c ≥7%). The patients in the group with mean serial $HbA1_C$ <7 percent served as the comparator group for analysis (see Figure 2.1).

2.3.1 Cohort Structure

Figure 2.1 Study Design Structure



2.3.2 Data Source

The data used in this study was obtained from the Travis County CommUnityCare™ clinics' electronic medical record (EMR). This database captures real-life, longitudinal data (provider notes, laboratory data and medications) on patients receiving primary care. Thirteen of the sixteen CommUnityCare™ clinics formerly called City of Austin clinics are located in Austin, Texas. They were established in 1970 by the Austin City Council in partnership with the Travis County Commissioner's Court

and officially earned a Federally Qualified Health Center (FQHC) status in 2001. The clinics provide primary care, dental care, and family planning services to over 50,000 indigent individuals in Travis County, with approximately 74 percent of patients being Hispanic, 12 percent Caucasian, 11 percent African American, and three percent other ethnicities.[59] The EMR was initiated in 2004, and by 2007, it was fully implemented in all clinics.

2.3.3 Study Population

Data was extracted from the CommUnityCare^{TM} database for the time period between October 1, 2004 and September 30, 2009. The year 2004 was used because it was when EMR implementation was initiated in CommUnityCare^{TM}, and to accommodate for early and late adopters of EMR within the CommUnityCareTM system, data was supplemented from other databases. The five-year time period of data extraction was used to maximize patient eligibility for the study.

The inclusion criteria that were used for selecting patients are as follows:

1. Type 2 diabetes patients aged between 30 and 80 years;
2. At least two years of continuous enrollment in the CommUnityCare^{TM} system;
3. At least one $HbA1_C$ value each year for a minimum of two consecutive years during the study period; and
4. No diagnosis of ACS or CA 6 months prior to the index date.

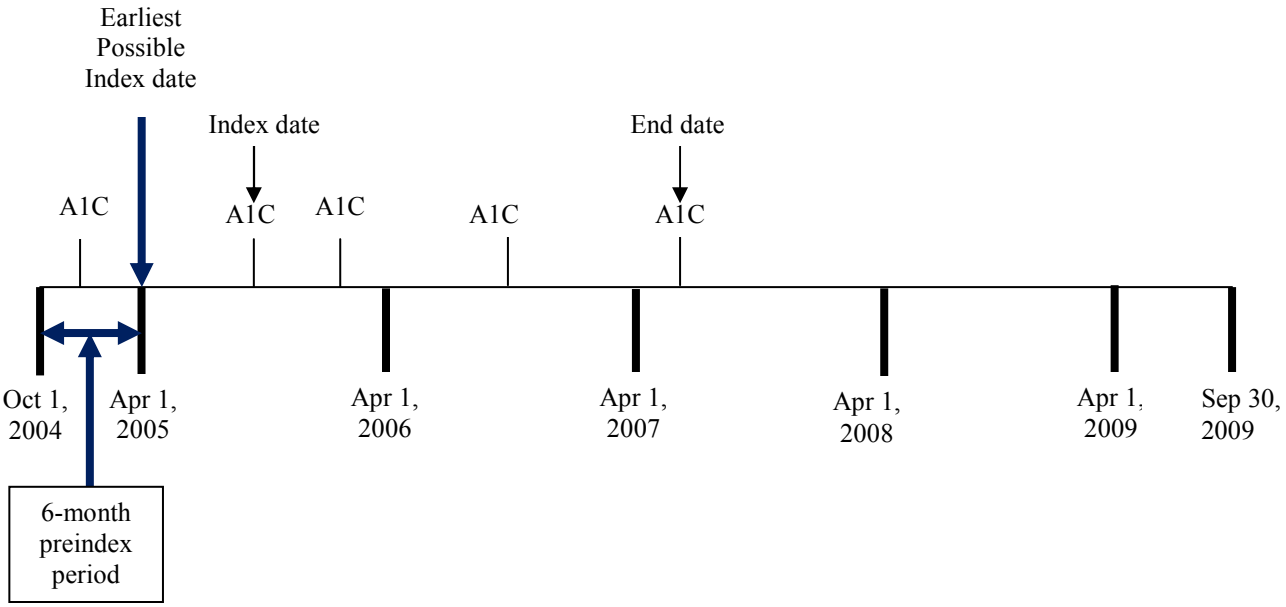
2.3.4 Study Cohorts, Index Date and Timeframe

Two cohorts were created from the study sample based on mean serial $HbA1_C$ values over the study period. The first cohort (comparator group) consisted of diabetic patients with mean serial $HbA1_C$ values less than 7 percent and the second cohort had patients with mean serial $HbA1_C$ values greater than or equal to 7 percent. The cohort structure is shown in Figure 2.1. The six-month period from October 1, 2004 to March 31, 2005 served as the 'wash-out' period. Any eligible patient who had the outcome (CA or ACS) during the six-month pre-index period was excluded. The earliest possible index date was April 1, 2005. The index date for the patients with the outcome (i.e., incident diagnosis of CA or ACS) was the date of the first of consecutive $HbA1_C$s prior to the date of outcome and the end date was the outcome date. The last consecutive $HbA1_C$ value must occur within 365 days prior to the outcome or on the day of the outcome. For patients without the outcome, the index date for eligible patients is the earliest of consecutive $HbA1_C$s and the end date is the last of consecutive $HbA1_C$s.

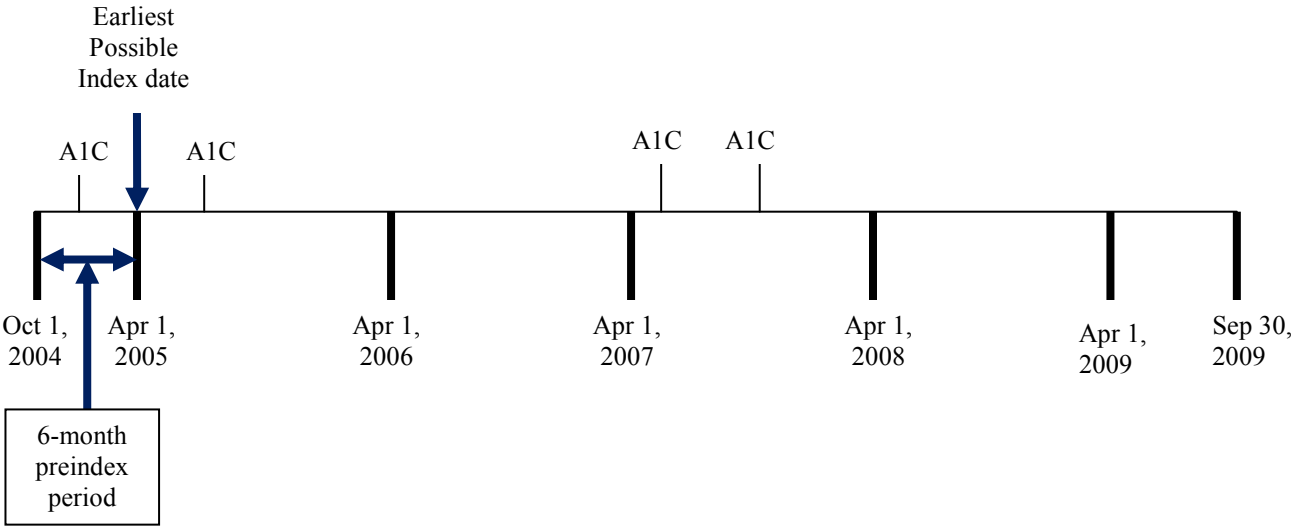
Eligible patients were followed for a minimum of two consecutive calendar years, but the criteria for the follow-up schedule and the index date differed for patients with the outcome and patients without the outcome. Figure 2.2 illustrates the different scenarios that may occur.

Figure 2.2 Study Follow-up Schedule

1. Patients without the outcome

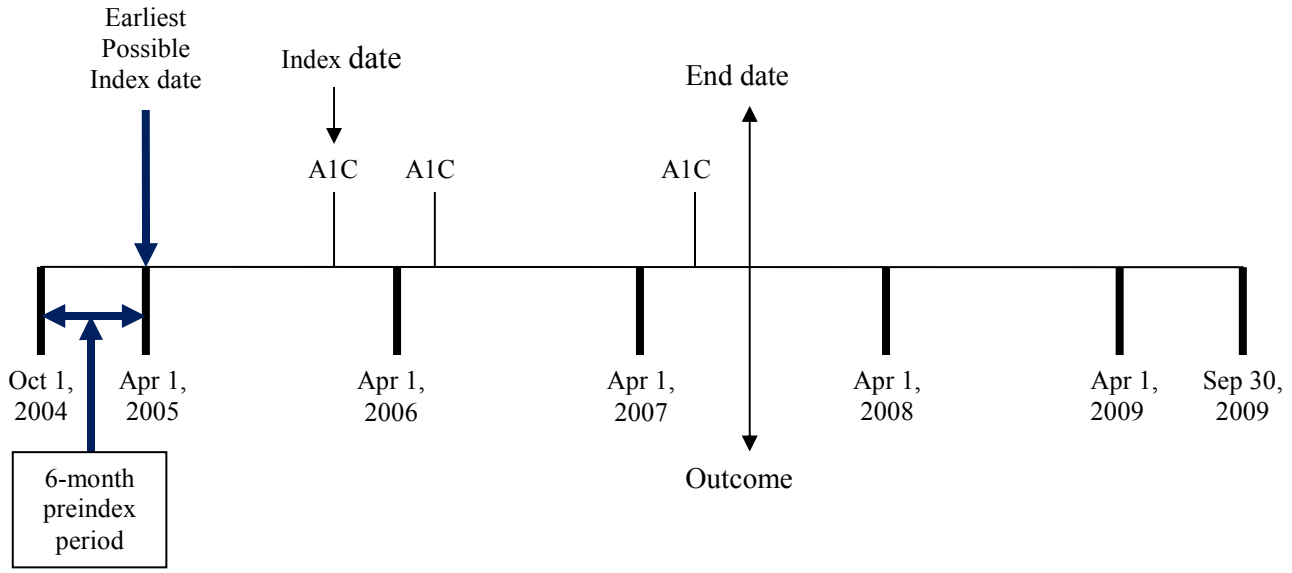


Included *because of two consecutive years of at least one* $HbA1_C$ *per year*

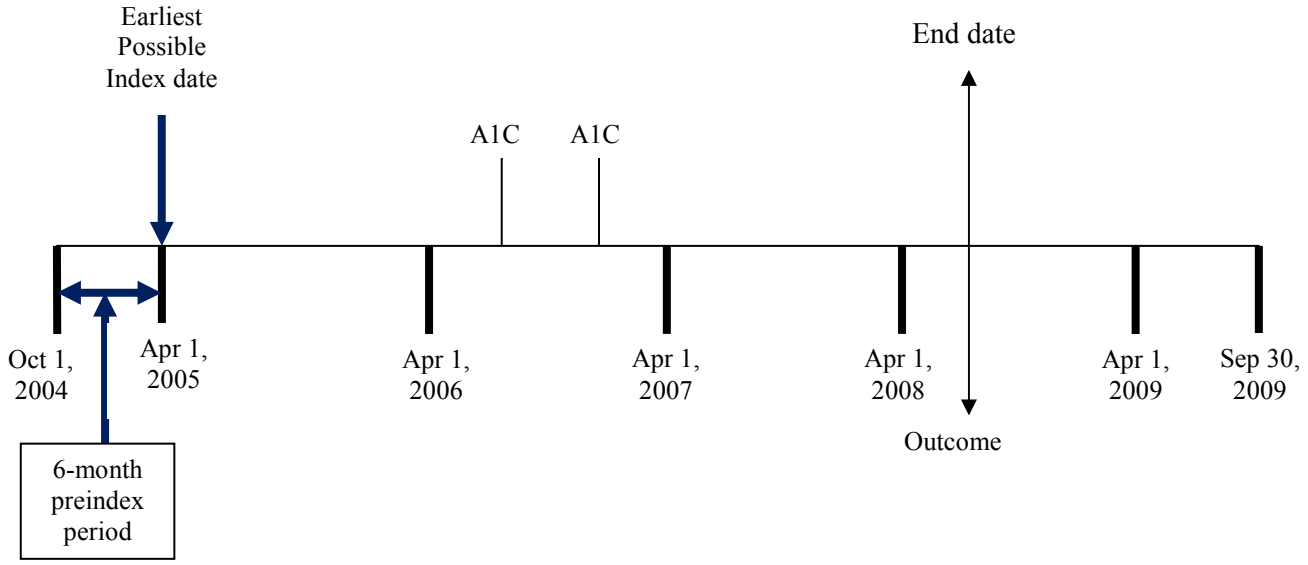


Excluded *because* $HbA1_C$ *values were not in consecutive years*

2. Patients with the outcome



Included *because at least two consecutive years of $HbA1_C$ prior to outcome*



Excluded *because no two consecutive years of $HbA1_C$ before the outcome*

2.4 STUDY ENDPOINTS

2.4.1 Primary Outcome

The primary outcome of the study was the risk (incidence) of CA or ACS in T2DM patients when the mean serial $HbA1_C$ <7 percent group was compared to the mean serial $HbA1_C$ ≥7 percent group, after adjusting for covariates (age, gender, hypertension, LDL-C, microalbuminuria, aspirin use, statin use, insulin use, tobacco use, and BMI). The comparator cohort mean serial $HbA1_C$ <7 percent was used in the study so that the study group with mean serial HbA1C ≥7 percent could be compared to the current standard of practice as recommended by the ADA. An odds ratio was calculated from logistic regression to evaluate the primary outcome.

2.4.1 Study Variables

The dependent variables were CA or ACS, which consisted of UA, NSTEMI and STEMI. The main independent variable of this study is $HbA1_C$ (dichotomized into <7% and ≥7% groups). The covariates were age, gender, hypertension, LDL-C, microalbuminuria, aspirin use, statin use, insulin use, tobacco use, and BMI. The study variables and operational definitions are listed in Table 2.1.

Table 2.1 Study Variables and Operational Definitions

Variable	Operational Definition	Code
Dependent		
ACS (UA, NSTEMI, STEMI) or CA	A diagnosis of any of the below: UA ICD-9: 411.1 & 413.9 NSTEMI ICD-9: 410.7 STEMI ICD-9: 410.0-410.6 & 410.8 CA ICD-9: 414.00-410.07	0= No 1= Yes
Independent		
$HbA1_C$	Mean $HbA1_C$ during the study period	0= <7% 1= ≥7%
Covariates		
Age	Age at index	Years (continuous)
Gender	Male or female	0= Male 1= Female
Hypertension	ICD-9: 401.1 or 401.9	0= No 1= Yes
LDL-C	LDL-C closest to end date	0= <100 mg/dL 1= ≥100 mg/dL
Microalbuminuria	Microalbuminuria closest to end date	0= <30 mg/g 1= 30-300 mg/g
Aspirin use	Any aspirin product used during study period	0= No 1= Yes
Statin use	Any statin used during study period	0= No 1= Yes
Insulin use	Any insulin product used during the study period	0= No 1= Yes
Tobacco use	Tobacco use reported during study period	0= No 1= Yes
BMI	BMI closest to the end date	1= <24.9 Kg/m^2 2= 25.0-29.9 Kg/m^2 3= 30.0 Kg/m^2

Abbreviations: ACS=acute coronary syndromes; BMI=body mass index; CA=coronary atherosclerosis; $HbA1_C$= glycated hemoglobin; LDL-C=low density lipoprotein cholesterol; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST-segment elevation myocardial infarction; UA=unstable angina

2.5 STATISTICAL ANALYSES

Continuous variables were reported as mean values ± SD. Frequencies and percentages were utilized to present categorical variables (Objective 1). In addition, a chi-square test was used to estimate the association between incident CA or ACS and each categorical covariate. Similarly, a t-test was used to estimate the association between incident CA or ACS and age. Pearson's chi- square test was used to estimate the association between incident CA or ACS and HbA_{1C} (Objective 2). Logistic regression was used to estimate the association (i.e., odds ratios with 95% CI) between incident CA or ACS and $HbA1_C$ while controlling for covariates (Objective 3). P-values <0.05 were considered statistically significant. The assumptions of the Pearson's Chi-Square tests are random sampling of the data, adequate cell sizes and independent observations. No assumption was made about the distribution of the independent variables in logistic regression. All statistical analyses were performed using SAS version 9.1.3. The independent and dependent variables and a summary of data analysis are presented in Table 2.2.

Table 2.2 Summary of Independent and Dependent Variables and Statistical Analyses

Hypothesis	DV	Measurement Level	IV	Measurement Level	Statistical Procedure
Objective 1: To describe the demographic and clinical characteristics of type 2 diabetic patients with CA or ACS (i.e., UA, NSTEMI, and STEMI)					
Hypothesis-None	ACS (UA, NSTEMI, STEMI) CA	Nominal (*dichotomous)* 0=No 1=Yes	$HbA1_C$ (<7% and ≥ 7%) <u>Covariates</u> Age Gender Hypertension LDL-C Microalbuminuria Aspirin use Statin use Insulin use Tobacco use BMI	Ordinal Continuous Nominal Nominal Ordinal Ordinal Nominal Nominal Nominal Nominal Ordinal	Descriptive statistics Descriptive statistics, t-test (age) and chi-square tests for each of the remaining covariates
Objective 2: To examine the relationship between incident diagnosis of CA or ACS and mean serial $HbA1_C$					
H_{02A1}: There is no statistically significant difference in incident diagnoses of CA or ACS between the $HbA1_C$ <7 percent and $HbA1_C$ ≥7 percent groups	ACS (UA, NSTEMI, STEMI) CA	Nominal (*dichotomous)* 0= No 1= Yes	$HbA1_C$ (<7% and ≥ 7%)	Ordinal	Chi-square
Abbreviations: ACS=Acute coronary syndromes; BMI=body mass index; CA=coronary atherosclerosis; DV=dependent variable; $HbA1_C$=glycated hemoglobin; IV=independent variable; LDL-C=low density lipoprotein cholesterol; NSTEMI=non-ST-segment elevation myocardial infarction; STEMI=ST- segment elevation myocardial infarction; UA=unstable angina					

Table 2.2 Summary of Independent and Dependent Variables and Statistical Analyses, cont.

Hypothesis	DV	Measurement Level	IV	Measurement Level	Test
Objective 3: To determine the associations of CA or ACS with mean serial $HbA1_C$ in T2DM patients after controlling for age gender, hypertension, LDL-C, microalbuminuria, aspirin use, statin use, insulin use, tobacco use and BMI					
$H_{03A1:}$: There is no statistically significant difference in incident diagnosis of CA or ACS between the $HbA1_C$ <7 percent and $HbA1_C$ ≥7 percent groups while controlling for covariates H_{03B1} - H_{03B10}	ACS (UA, NSTEMI, STEMI) CA	Nominal (*dichotomous)*	$HbA1_C$ <7% and $HbA1_C$ ≥7% <u>Covariates</u> Age Gender Hypertension LDL-C Microalbuminuria Aspirin use Statin use Insulin use Tobacco use BMI	Ordinal Continuous Nominal Nominal Ordinal Ordinal Nominal Nominal Nominal Nominal Ordinal	Logistic regression
Abbreviations: ACS=Acute coronary syndromes; BMI=body mass index; CA=coronary atherosclerosis; DV=dependent variable; $HbA1_C$=glycated hemoglobin; IV=independent variable; LDL-C=low density lipoprotein cholesterol; NSTEMI=non-ST-segment myocardial infarction; STEMI=ST- segment myocardial infarction; UA=unstable angina					

2.5.1 Sample Size Calculation

To address Objective 2, a chi-squared analysis was performed and Objective 3 employed logistic regression. Since logistic regression required the larger sample, the formula below was utilized to determine the sample size [60]:

$$N = \frac{1}{[p(1-R)]^2}\left[Z_{1-\alpha}\sqrt{\left(1+\frac{1}{K}\right)U(1-U)} + Z_{1-\beta}\sqrt{pR(1-Rp)+\frac{p(1-p)}{K}}\right]^2 \qquad U = \frac{Kp+pR}{K+1}$$

Where:

N=Number of subjects in the exposed group

P=Incidence of the disease in the control population/year

R=Minimum relative risk to be detected

α=Type I error

β=Type II error

K=ratio of the number of subjects in the unexposed group to the number of subjects in the exposed group

The α was set at 0.05 and β at 0.2 (resulting in 80% power). Based on Avogadro et al., the incidence rate of first CHD event per 1,000 person-years among T2DM patients was 28.8 (95% CI 5.4–32.2) in men and 23.3 (20.2–26.4) in women.[61] Thus, we examined calculated sample size based on minimum relative risk of 1.25, incidence of the disease in the unexposed at two percent, and used a ratio (2:1) of subjects in unexposed and exposed groups. Based on these values, a minimum sample size of 2436 subjects

with 812 subjects being in the exposed cohort was needed to address the study objectives. The study setting, CommUnityCare™ clinics have a diabetes population aged 30 to 80 years of approximately 9,800.

Table 2.3 Sample Size Calculation

Incidence	2%
Relative risks	1.25
Ratio of unexposed:exposed	2:1
Sample size (unexposed:exposed)	1624:812
Total sample size	2436

CHAPTER THREE: RESULTS

3.1 CHAPTER OVERVIEW

Chapter Three describes the demographic and clinical characteristics of the study population and results of the study objectives. The selection of subjects meeting the inclusion and exclusion criteria will be provided. Then, descriptive analyses of the demographic and clinical variables for the eligible patients will be presented. Finally, the unadjusted results of the chi-square analyses and the adjusted results of the logistic regression analyses that examined the relationship between $HbA1_C$ and incident diagnosis of CA and ACS will be presented.

3.1.1 Included Patients and Demographic Characteristics

Data for this study was obtained from the Travis County CommUnityCare™ clinic database for the time period October 1, 2004 to September 30, 2009. The six-month period from October 1, 2004 to March 31, 2005 served as the 'wash-out' period. The profiles of 9838 T2DM patients were retrieved. After applying the inclusion criteria, a total of 3069 patients were included in the final sample (see Table 3.1). The main reason for excluding eligible patients was lack of continuous enrollment (N=3297) followed by the inclusion criterion of at least one $HbA1_C$ value each calendar year for a minimum of two consecutive years during the study period (N=2673).

Table 3.1 Selection of Patients Meeting Inclusion/Exclusion Criteria

Reason for Exclusion	Number Deleted	Number Remaining
Number of T2DM patients		9838
Lack of continuous enrollment for at least two consecutive years between April 1, 2005 and September 30, 2009	[3297]	6541
Lack of at least one $HbA1_C$ value each year for two consecutive years	[2673]	3868
Number of patients with a diagnosis of ACS or CA 6 months prior to index date	[55]	3813
Number of patients with diagnosis of ACS or CA more than 1 year after of the last consecutive $HbA1_C$ date	[107]	3706
Number of T2DM patients <30 or >80 years old	[186]	3520
Number with casewise missing values	[451]	3069

3.2 OBJECTIVES

3.2.1 Objective 1 Analysis (Descriptive Statistics)

Objective 1 describes the outcome, demographic and clinical characteristics of T2DM patients included in the study sample. Regarding the outcome variable, the majority (98%) of patients (N=3007) did not have a diagnosis of CA or ACS, while only two percent (N=62) had a diagnosis of CA or ACS. The descriptive statistics for primary independent variable (i.e., $HbA1_C$) and covariates for the entire sample (N=3069) and the two cohorts (i.e. with and without incident CA or ACS) are shown in Table 3.2. The

entire sample statistics will be described, followed by a highlight of significant differences between the two cohorts.

The mean ± SD $HbA1_C$ of all patients was slightly over the ADA recommended value (<7.0%) at 7.8%±1.7%. The mean ± SD age of patients was 53.6±11.2 years, and females represented almost two-thirds (64.2%) of the entire cohort. Hypertension (defined by ICD-9 codes 401.1 or 401.9) was present in the majority (81.2%) of patients and slightly over one-third (35.0%) had LDL-C levels ≥100 mg/dL. A history of microalbuminuria > 300 mg/g was observed in 29.2 percent of patients. Almost 45 percent (44.6%) of patients had a history of aspirin use during the study period, while two-thirds (66.6%) were prescribed a statin. The proportion of patients who received insulin was 33.5 percent and 12.5 percent used tobacco during the study period. Less than ten percent (9.5%) of patients were underweight to normal weight (BMI ≤ 24.9 kg/m^2), 26.8 percent were overweight (BMI range 25.0-29.9 kg/m^2), and the majority of patients (63.7%) were obese (BMI ≥30.0 kg/m^2). Among bivariate comparisons of independent variables and the outcome, there were three variables that were significant. A t-test showed that patients with CA or ACS were significantly ($p<0.0001$) older than those without CA or ACS (59.0±8.9 years vs. 53.4±11.2 years, respectively). A chi-square analysis revealed a significantly ($p=0.0367$) lower percentage of males with CA or ACS compared to males without CA or ACS. Of those patients with CA or ACS, 48.4 percent were males while only 35.6 percent of patients without CA or ACS were males. Additionally, a chi-square analysis revealed a significantly ($p=0.0001$) higher percentage

of patients with hypertension among those with CA or ACS (100%) compared to those without CA or ACS (80.8%).

Table 3.2 T-test and Chi-Square Analyses of Patient Variables by Outcome

Variables	All N=3069 (100.0%)	CA or ACS Yes N=62 (2.0%)	CA or ACS No N=3007 (98.0%)	Test Statistic	Df	p-value
$HbA1_C$ (Mean ± SD)	7.8 ± 1.7	7.6 ± 1.5	7.8 ± 1.7	0.94[a]	3067	0.3463
Age in years (Mean ± SD)	53.6 ± 11.2	59.0 ± 8.9	53.4 ± 11.2	4.82 [a]	65	<0.0001
Male (%)	35.8	48.4	35.6	4.35[b]	1	0.0367
Hypertension (%)	81.2	100.0	80.8	14.62[b]	1	0.0001
LDL-C≥100 mg/dL (%)	35.0	27.4	35.1	1.58[b]	1	0.2083
Microalbuminuria[c] (%)	29.2	30.7	29.1	0.07[b]	1	0.7953
Aspirin use (%)	44.6	41.9	44.7	0.19[b]	1	0.6652
Statin use (%)	66.6	71.0	66.5	0.53[b]	1	0.4647
Insulin use (%)	33.5	32.3	33.5	0.04[b]	1	0.8347
Tobacco use (%)	12.5	12.9	12.5	0.01[b]	1	0.9188
BMI						
≤24.9 (%)	9.5	1.6	9.7	4.66[b]	2	0.0974
25.0-29.9 (%)	26.8	30.7	26.7	-	-	-
≥30.0 (%)	63.7	67.7	63.6	-	-	-

Abbreviations: ACS=acute coronary syndromes; BMI=body mass index; CA=coronary atherosclerosis; $HbA1_C$=glycated hemoglobin; LDL-C=low density lipoprotein cholesterol

[a] T-test
[b] Chi-Square Test
[c]Microalbuminuria defined as urine albumin/creatinine ratio ≥ 30 mg/g

3.2.2. Objective 2 Analysis (Chi-Square)

Objective 2 was to examine the unadjusted relationship between incident CA or ACS and $HbA1_C$. A chi-square test (see Table 3.3) revealed no significant relationship between incident CA or ACS and $HbA1_C$ (χ^2 =0.30; df=1; p=0.5834). Patients with incident CA or ACS had a slightly smaller proportion with $HbA1_C$ ≥7% compared to those without CA or ACS (58.1% vs. 61.5%, respectively). The null hypothesis [H_{02A1}: *There is no statistically significant difference in incident diagnoses of CA or ACS between the* $HbA1_C$ *<7 percent and* $HbA1_C$ *≥7 percent groups*] was not rejected.

Table 3.3 Chi-Square Analysis of Incident CA or ACS and $HbA1_C$

	CA or ACS			
$HbA1_C$	Yes N	(%)	No N	(%)
<7%	26	41.9	1158	38.5
≥7%	36	58.1	1849	61.5
Total	62	100.0	3007	100.0
Abbreviations: ACS=acute coronary syndromes; CA=coronary atherosclerosis; $HbA1_C$=glycated hemoglobin				

χ^2 =0.30, df=1, p=0.5834

3.2.3. Objective 3 Analysis (Logistic Regression)

Logistic regression was used to determine the association between incident CA or ACS and $HbA1_C$ (i.e., <7% compared to ≥7%) in T2DM patients after controlling for age gender, hypertension, LDL-C, microalbuminuria, aspirin use, statin use, insulin use, tobacco use and BMI (See Table 3.4). The overall logistic regression model was significant (χ^2=30.51, df=11, p=0.0013); however, there was no significant difference between incident CA or ACS and $HbA1_C$ [Odds Ratio (OR)=1.026, 95% CI=0.589-1.785, p=0.9289]. The null hypothesis [H_{03A1}: *There is no statistically significant difference in incident diagnoses of CA or ACS between the* $HbA1_C$ *groups (i.e., <7% compared to ≥7%), while, controlling for covariates*] was not rejected.

Covariate analyses results are detailed below with associated hypothesis test results shown in Table 3.4. Note: Hypertension was deleted from the logistic regression model because all subjects with incident CA or ACS had hypertension (see Table 3.2), thereby making the logistic regression model unstable. Age was significantly related to incident diagnosis of CA or ACS (OR=1.051, 95% CI=1.025-1.077, p<0.0001). For each one year increase in age, subjects were 5.1 percent more likely to have incident CA or ACS. Gender was significantly related to incident diagnosis of CA or ACS (OR=1.855, 95% CI=1.105-3.115, p=0.0195). Compared to females, males were 85.5 percent more likely to have incident diagnosis of CA or ACS. Low density lipoprotein cholesterol was not significantly associated with incident CA or ACS (OR=1.262, 95% CI=0.712-2.237, p=0.4253), nor was microalbuminuria (OR=1.029, 95% CI=0.583-1.816, p=0.9220). Aspirin use during the study period was not significantly related to incident CA or ACS (OR=1.286, 95% CI=0.764-2.162, p=0.3438). Similarly, statin use during the study period was not significantly related to incident CA or ACS (OR=0.932, 95% CI=0.529-

1.642, p=0.8081). Neither insulin use (OR=0.983, 95% CI=0.547-1.767, p=0.9554) nor tobacco use (OR=0.808, 95% CI=0.375-1.742, p=0.5858) during the study period were not significantly related to incident CA or ACS. Compared to obese patients (BMI ≥ 30.0 kg/m^2) those who were under to normal weight (BMI <25.0 kg/m^2), were 87.8 percent less likely to be diagnosed with incident CA or ACS (OR=0.122, 95% CI=0.017-0.895, p=0.0438). However, there was no significant difference in incident CA or ACS between overweight (BMI 25.0-29.9 kg/m^2) and obese patients (OR=0.885, 95% CI=0.505-1.550, p=0.0963).

Table 3.4 Logistic Regression Analyzing the Association of Mean $HbA1_C$ With Incidence of CA or ACS in T2DM Patients after Controlling for Covariates

Variable[a]	Odds Ratio	95% CI	Wald χ^2	p-value	Hypothesis Result[b]
$HbA1_C$ <7%	1.026	0.589-1.785	0.008	0.9289	Not Rejected
Age	1.051	1.025-1.077	15.531	*<0.0001*	Rejected
Male	1.855	1.105-3.115	5.460	*0.0195*	Rejected
LDL-C<100mg/dL	1.262	0.712-2.237	0.636	0.4253	Not Rejected
Normoalbuminura	1.029	0.583-1.816	0.010	0.9220	Not Rejected
Aspirin nonuse	1.286	0.764-2.162	0.896	0.3438	Not Rejected
Statin nonuse	0.932	0.529-1.642	0.059	0.8081	Not Rejected
Insulin nonuse	0.983	0.547-1.767	0.003	0.9550	Not Rejected
Tobacco nonuse	0.808	0.375-1.742	0.297	0.5858	Not Rejected
BMI (kg/ m^2)					
<25.0	0.122	0.017-0.895	4.065	*0.0438*	Rejected
≥25.0-29.9	0.885	0.505-1.550	2.766	0.0963	Not Rejected

Abbreviations: ACS=acute coronary syndromes, BMI=body mass index, CA=coronary atherosclerosis, $HbA1_C$=glycated hemoglobin, LDL-C=low density lipoprotein cholesterol

[a]Reference groups: $HbA1_C \geq 7\%$; female; LDL-C ≥ 100 mg/dL; microalbuminuria (urine albumin/creatinine ratio ≥ 30 mg/g); BMI ≥30.0 kg/m^2 [*Note: SAS used the highest coded number for each categorized variable as default reference group*]

[b] Hypotheses were stated in the null form

Overall model χ^2=30.51, df=11, p=0.0013

CHAPTER FOUR: DISCUSSION

4.1 CHAPTER OVERVIEW

The results are discussed in this chapter, along with the strengths and limitations of the study, and the study conclusion is presented.

4.2 REVIEW OF STUDY BACKGROUND AND OBJECTIVES

The leading cause of morbidity and mortality among diabetic patients is CVD.[14] Cardiovascular diseases which consist of CHD, stroke, PVD, hypertension and congestive heart failure [3] accounted for approximately 68 percent of deaths in diabetic patients in 2004, with CHD as the leading cause.[6] Coronary heart disease consists of acute coronary syndromes (ACS) which include UA, AMI, and small vessel coronary artery disease(CAD).[4-5] After Haffner et al. reported that diabetic patients with no prior CAD had the same risk of developing MI as a non-diabetic with established CAD, the NCEP revised its lipid guidelines to classify diabetes as a CAD risk equivalent, with a 10-year cardiovascular event risk greater than 20 percent.[7, 9]

To reduce diabetes morbidity and mortality, the ADA recommends targeting $HbA1_C$ values below seven percent in diabetic patients using a combination of lifestyle and pharmacotherapy interventions.[14] In addition, the ADA recommends aggressive

management of other cardiovascular risk factors such as hypertension, high LDL-C, microalbuminria and obesity in diabetic patients.

Although studies have shown a trend of decreasing incidence of cardiovascular outcomes with aggressive management of diabetes (i.e., treating to target FBS or $HbA1_C$), the reduction in cardiovascular outcomes has not been significant even in well designed RCTs that compared intensive blood glucose control to standard control.[47-49, 53-54]. With the ACCORD study, the rapid decrease in blood glucose over the first year in the intensive arm of study was hypothesized to be the cause of increased mortality, which eventually led to the premature discontinuation of the study after approximately three and one-half years. With atherosclerosis, studies including diabetic subjects have shown a significant association between long-term diabetes and negative changes in the vascular wall (IMT and CCA).[37, 46]

Little is known about the association between mean serial $HbA1_C$ values preceding an atherosclerotic coronary event and the occurrence of the coronary event. The aim of this study was to determine the significance of mean serial $HbA1_C$ in predicting incident CA or ACS in T2DM patients by comparing a cohort with mean serial $HbA1_C$ <7 percent as recommended by the ADA, to a cohort with mean serial $HbA1_C \geq 7$ percent. The analyses conducted to address the study aim used "real-world" longitudinal data of indigent patients receiving routine primary care through the Travis County CommUnityCare™ clinics in Austin, Texas and its surrounding suburbs.

4.3 STUDY FINDINGS

4.3.1 Objective 1

This objective described the outcome (CA or ACS), demographic and clinical characteristics of T2DM patients included in the analyses. Although the mean age of patients in this study was younger (54 years), there was a higher prevalence of females (64%) when compared with other studies. Recent studies (ACCORD, ADVANCE and VADT) which examined the relationship between blood glucose control and cardiovascular outcomes had study samples of patients with ages ranging from 60-66 years and with less than half of the samples comprised of females.[37, 46, 49, 53-54] Although race/ethnicity data was not collected, the CommUnityCare^{TM} patient population is predominantly Hispanic (74%), with approximately equal proportions of African Americans and Caucasians comprising the remaining population. Because diabetes is more prevalent in minority populations and because of the race/ethnicity distribution of the clinic population, we are confident that the majority (>50%) of patients in this study were minority. In the ACCORD and VADT studies, Hispanics comprised 16 percent and 7.2 percent, respectively, while the DCCT had only four percent minority subjects. [47, 53-54]. In summary, the demographic characteristics of this study sample differ compared to other notable studies of diabetes that evaluated cardiovascular event outcomes. Specifically, this study's patients were younger, and predominantly female and minority.

The mean ± SD $HbA1_C$ of patients in this study was 7.8±1.7 percent, which was higher than the baseline $HbA1_C$ level for the ADVANCE study (7.5 ± 1.6%), but lower than baseline $HbA1_C$ levels in the ACCORD (8.3±1.1%) and VADT (9.4 ± 2.0%) studies.[47, 53-54] The high $HbA1_C$ for the VADT cohort at baseline was because it

included subjects who responded poorly to maximal doses of oral antidiabetic agents and excluded those with $HbA1_C$ <7.5 percent at enrollment. Among the clinical covariates controlled for in this study, only the proportion of subjects with hypertension (defined by ICD-9 codes 401.1 or 401.9), differed significantly ($p<0.05$) between individuals with the outcome (100.0%) and individuals without the outcome (80.8%). The proportion of hypertensive patients in the total sample was 81.2 percent which was higher than the VADT (72%) study. The proportion of hypertensive patients was not provided by the ACCORD, ADVANCE, DCCT and UKPDS studies; instead, those studies presented averages of systolic and diastolic pressures.[47-48, 53-54].

Regarding the other clinical covariates, two-thirds of the sample used statin medications (66.6%) and 64 percent of subjects were obese with a mean BMI±SD of 33.8±8.3 kg/m^2. The proportion of the sample that used a statin was similar to the ACCORD study (62%), but higher than the ADVANCE study (47% at the end of follow-up).[[49, 54] Mean BMI values in this study were similar to the VADT and ACCORD studies (31.3 kg/m^2 and 32.5 kg/m^2, respectively), but higher than the ADVANCE (28.5 kg/m^2) study, which included subjects from Europe, Australia and Asia, in addition to North America.[49, 53-54]

The following covariates were observed in less than 50 percent of this study's sample: LDL-C ≥100 mg/dL, microalbuminuria, aspirin use, insulin use and current tobacco use. This study had 35 percent of the total sample and 27.4 percent of those with the outcome (CA or ACS) with LDL-C ≥100 mg/dL closest to their respective end dates. The high percentage of statin use (67%) could explain why 65 percent of the sample had LDL-C <100 mg/dL, which is the goal set by the ADA and the National Cholesterol Education Program (NCEP) to improve cardiovascular outcomes.[9, 14] Other studies reported mean LDL-C values that were at or close to the goal set by the

ADA.[49, 53-54] In the VADT, the mean LDL-C at the end of follow-up was 80 mg/dL, lower than what was reported for the ADVANCE (102 mg/dL) and ACCORD (105 mg/dL) studies. The proportion of subjects who used a statin in this study (67%) is similar to the ACCORD (62%) study, but higher than the multi-continental ADVANCE study which had 47 percent of its subjects using a statin at the end of follow-up period.

Microalbuminuria was present in 29 percent of subjects in this sample, which is slightly higher than the microalbuminuira history recorded in the ADVANCE study (27%). After a maximum follow-up of seven years in the VADT study, 11.5 percent of subjects progressed from normoalbuminuria to microalbuminuria, but standard therapy and intensive therapy did not differ significantly in the rate of progression.[53]

The rate of aspirin use (44.6%) in this study was lower than what was reported in the ACCORD study (54.5%), which was an epidemiologic study conducted in 10,251 patients in the US and Canada.[54] However, aspirin use was similar to the ADVANCE study at baseline (43.8%), but not the end of follow-up where the reported use of aspirin rose to 56 percent.[49] VADT used a more aggressive approach for aspirin use and prescribed aspirin for all enrolled subjects unless contraindicated.[53] The reason why less than half of this study sample was not on aspirin could be explained by under-reporting of aspirin use by subjects who are required to purchase aspirin over-the-counter (versus receiving aspirin through the clinic) for cardiovascular prophylaxis. Since the study follow-up period ended in September 2009, the low rate of aspirin use was not a result of the recommendations by the ADA guideline taskforce in November 2009 to curtail aspirin use to only high-risk diabetic patients.[14]

Approximately one-third of the CommUnityCare^{TM} study sample (33.5%) used insulin as part of their diabetes regimen, which was similar to the ACCORD cohort at baseline (34.9%).[54] Since ACCORD recruited patients throughout the US, the

proportion of patients on insulin in its large sample (10,251 patients) provided a broad "snapshot" of insulin use across various medical practices nationwide. Hence CommUnityCare™ health professionals' insulin prescribing patterns are similar to other providers across the country. Similarly, the VADT sample, with a higher mean $HbA1_C$ at enrollment (9.4%) had a baseline insulin use of 35 percent. On the contrary, the ADVANCE sample had baseline insulin use of 1.5 percent which increased to 40 percent in the intensive arm at the end of follow-up.[49, 53] This number may have been low at baseline due to an exclusion criterion of having a definite indication for insulin for long-term treatment at the time of enrollment.

The smoking rate in this study sample was 12.5 percent which was lower than in the following studies: ACCORD (14%), ADVANCE (14%), VADT (17%), UKPDS (31%), and DCCT (18%).[47-49, 53-54] Perhaps the UKPDS study had current tobacco use approximately twice that of ACCORD and ADVANCE because at the time that the UKPDS study was started (1977), smoking cessation was not a focus in the prevention of cardiovascular events.[48-49, 54]

In summary, for each covariate (demographic or clinical characteristic) in this study, there were one or more prospective studies with similar characteristics, with the exception of race and gender. Education, mean duration of diabetes, previous cardiovascular event, other antiplatelet agents, oral hypoglycemic agents and waist circumference were matching variables in some of the prospective studies. However, these were not included in the present study.

The rate of the outcome (CA or ACS) in this study was two percent over a mean follow-up of approximately 2 years (1.8 years), which is lower than reported by Avogadro et al. (1.9% per year) and the Atherosclerosis Risk in Communities Study (ARIC) (1.4% per year).[61-62] Both Avogadro et al. and ARIC were prospective cohort

studies to determine incidence of CHD in diabetic patients and they followed diabetic patients for longer periods of time (minimum of 4 and 8 years respectively) compared to this study. Also, Fox et al. calculated from the original cohort of the Framingham risk study (which the NCEP ATP III guidelines for prevention of cardiovascular disease were based), a ten-year risk odds ratio of CVD of 21.6 percent (95% CI=9.5-33.6) for females and 28.2 percent (95% CI=15.4-41.1) for males with diabetes respectively.[63] Another reason for the lower event rates in this study could be explained by the narrow definition of the outcome using ICD-9 codes for CA or ACS. Avogadro et al. included patients with coronary vessel occlusion who had undergone coronary artery bypass graft or percutaneous transluminary coronary angioplasty.[61] Furthermore, ACCORD, ADVANCE and VADT had 32-40 percent of the study population with prior history of CVD, which put them at a higher risk for a subsequent cardiovascular event.[49, 53-54] Finally, the lower incidence rate of the outcome in this study could be explained by aggressive management of cardiovascular risk factors (lower rates of smoking, statin use and LDL-C management). Having data on diabetic retinopathy (an independent risk factor for cardiovascular complications in diabetic patients) could have provided a better perspective of the risk of macrovascular complications of this study sample since retinoapathy can be present in diabetic patients at the time of diabetes diagnosis.[23] The higher proportion of females (64.2%) compared to males in this study (35.8%) may also account for the low incidence rate of the outcome since females have a higher risk of CA or ACS compared to males.

4.3.2 Objective 2

This objective examined the bivariate unadjusted relationship between the outcome (CA or ACS) and $HbA1_C$. Although a chi-square test did not show a significant relationship (p=0.5834) between CA or ACS and dichotomized mean serial $HbA1_C$, subjects with mean $HbA1_C \geq 7$ percent had a higher percentage of subjects with incident CA or ACS compared to those with $HbA1_C < 7$ percent (58.1 vs. 41.9). Insufficient power may explain why the results were not significant in the present study. However, other large prospective randomized studies (N=1441-11140) did not find a significant difference in the incidence of CVD and tight glycemic control.[47-49, 53-54]

Contrary to the nonsignificant chi-square analysis in this study, unadjusted analyses from two prospective studies (ACCORD and UKPDS) showed significant associations between cardiovascular event outcomes and $HbA1_C$. The ACCORD researchers conducted a subgroup analysis in which they evaluated the unadjusted relationship between the primary outcome (a composite of MI, stroke, and death from cardiovascular causes) and baseline $HbA1_C$ and found a significant relationship (increased risk) between the primary outcome and baseline $HbA1_C$ (i.e., ≤8% compared to >8%). Similarly, Stratton et al reported an increasing ten-year risk for cardiovascular events with increasing mean updated $HbA1_C$ categories (i.e., <6%, 6-<7%, 7-<8%, 8-<9%, 9-<10% and ≥10%) in an unadjusted regression model using the UKPDS data.[63] Using the lowest $HbA1_C$ category as a reference, the risk of each of the clinical outcomes (any complications or death related to diabetes and all cause mortality, myocardial infarction, stroke, lower extremity amputation and microvascular disease) rose with mean updated $HbA1_C$ before and after adjustment for age, sex, ethnic group, lipid

concentration, smoking, blood pressure and albuminuria. Thus, this study's results are congruent with the majority of studies conducted that examined the relationship between $HbA1_C$ and CA or ACS.

4.3.3 Objective 3

Objective 3 assessed the association between the outcome (incident CA or ACS) and mean serial $HbA1_C$ (i.e., <7% compared to ≥7%) in the study sample after controlling for age, gender, hypertension, LDL-C, microalbuminuria, aspirin use, statin use, insulin use, tobacco use and BMI. The results showed no significant association between the incidence of CA or ACS in T2DM patients and mean serial $HbA1_C$. The results of the logistic regression supports the lack of significant association between $HbA1_C$ and cardiovascular outcomes found in several larger prospective studies that controlled for multiple risk factors. [17, 47-49, 53-54, 64]

Regarding the covariates, only three were significantly related to the outcome. Increasing age, male gender and BMI ≥ 30 kg/m^2 (compared with BMI <25 kg/m^2) were significantly associated with incident CA or ACS. Age, gender, LDL-C and hypertension diagnosis were cardiovascular risk factors that differed significantly at baseline between diabetic patients who developed incident CHD and those who did not in the ARIC epidemiological study, which followed 1,626 diabetic patients for eight years.[62]. Among the 186 incident CHD events reported (incidence rate = 11.4%) in the ARIC study, participants with incident CHD were older at baseline (mean age at baseline of 57 years), and more likely to be male (57%) when compared with diabetic cohort with no

events ($p<0.001$ for both comparisons). However, in the ARIC study, BMI (31 kg/m^2) at baseline was similar between the diabetic subjects who developed incident CHD and the diabetic subjects who did not over the study period.[62] Nevertheless, the impact of obesity (BMI $\geq$ 30 kg/m^2) on CVD risk should not be ignored based on the findings of Fox et al. who evaluated data from the Framingham heart study. The Framingham heart study was an epidemiological risk study conducted in predominantly white middle class subjects in Framingham, MA. The study examined the ten-year risk of developing CVD and found that among diabetic patients, CVD was higher in obese subjects compared to normal weight individuals. In normal weight diabetic men and women, the ten-year risks (HR, 95% CI) of developing CVD were 33.2 (6.3-60.0) and 9.4 (0.0-22.1) respectively; while in obese subjects, the risks increased to 47.6 (12.1-83.2) and 41.9 (14.2-69.6), respectively.[63]

The lack of significant risk reduction in outcome (per logistic regression) by the interventions targeted at cardiovascular risk reduction (aspirin use, statin use, nonsmoking, LDL-C < 100 mg/dL, and normoalbuminuria) may be due to lack of power in this study. These factors are among the primary preventive interventions to reduce cardiovascular complications in T2DM patients.[14]. The landmark Steno-2 study, which was conducted in T2DM patients with microalbuminuria in Denmark, reported that comprehensive multifactorial interventions (blood pressure, blood glucose, lipid control, ACE inhibitor use, aspirin use, smoking cessation, healthcare provider education and motivation, and lifestyle changes) reduced the risk of cardiovascular and microvascular complications by 50 percent, with the benefits persisting five years after the study follow-

up.[17, 65] Also, the Copenhagan male study showed that high TG and low HDL-C commonly seen in T2DM patients was as powerful predictor of CHD as LDL-C alone.[33] It is therefore important for clinicians to follow a multifactorial interventional approach as was employed in the Steno-2 study, in addition to glycemic control in T2DM to comprehensively reduce incidence of CVD.

Since this study used data from "real-life" patient follow-up, it is possible that patients who were treated aggressively for their diabetes to lower $HbA1_C$ levels were also the patients who were already at the highest risk for CVD at the time of diabetes diagnosis. If that was the case, then aggressively treating their diabetes to a lower $HbA1_C$ target, while concurrently targeting cardiovascular risk factors were not enough to avert the incidence of the outcome as was observed in the ACCORD subgroup analysis, which showed that increased mortality in the intensive group with target $HbA1_C$ <6.5 percent was higher among patients at high risk (prior history of CVD) at baseline.[54]

In the era of rising healthcare costs, it is important to consider the benefit or risk reduction attained from lowering $HbA1_C$ to currently recommended targets. Such information will be beneficial in budgeting the use of healthcare dollars especially for the minority population, who have a higher incidence of CVDs. It is also important to consider when serving patients who are indigent and/or who depend on public funding for their health needs, such as the CommUnityCare™ patients. From the author's experience in clinical practice, treating diabetic patients and helping them maintain ADA target $HbA1_C$ levels require significant healthcare resources (e.g., medications, insulin, glucometer, lancets, test strips, laboratory tests and medical interventions for

hypoglycemia). Patients must also contribute significant effort and commitment to lifestyle changes and medication adherence. Therefore, if the benefit of $HbA1_C$ reduction in decreasing CVD risk in certain categories of patients (e.g., shorter life expectancy, history of hypoglycemia requiring medical care, established microvascular and macrovascular complications), is not comparable to the cost involved, then resources may need to be channeled to treat other nonglycemic cardiovascular risk factors.

Finally, this study included atherosclerosis (a precursor to CVD) as an endpoint and did not find an association between mean serial $HbA1_C$ over two years and incidence of CA or ACS. This is contrary to the prospective studies which use hard endpoints of clinical events such as MI, CHD (ACS), stroke and even death. It may be beneficial (medically and economically) to identify the existence of subclinical asymptomatic disease (e.g., atherosclerosis) in order to start early management and avert additional morbidity (from CVD event which have irreversible damage) or mortality. One such study, MESA (Multi-Ethnic Study of Atherosclerosis), is examining these issues. The ongoing epidemiologic study includes a more diverse population (38% white, 28% African American, 23% Hispanic and 11% Asians) and it aims to provide insight regarding which risk factors of atherosclerosis are more important to target, and what interventions (pharmacologic and lifestyle) in "real-world" longitudinal primary care will slow or totally prevent the progression from subclinical atherosclerosis to overt CHD events.[66] The NCEP ATP III guidelines for predicting the ten-year risk for atherosclerosis and CVD from cardiovascular risk factors for appropriate prophylactic interventions was based on the data from the Framingham study with predominantly

white subjects. Similarly, the ten-year prospective cohort-diverse MESA study might provide information about whether $HbA1_C$ should be added to the cardiovascular risk prediction charts.

4.4 STUDY LIMITATIONS

In spite of having several strengths such as a predominant Hispanic population and a fairly comprehensive database for clinical and demographic factors, this study has several limitations. First, race was not adjusted for in this study as was done with most of the prospective diabetes studies evaluating cardiovascular outcomes. However, since approximately three-quarters of the population served by CommUnityCare™ are Hispanic, these results are generalizeable to the low-income Hispanic population who were seen for approximately two years by a CommUnityCare™ network provider. A second limitation is the accuracy and completeness of ICD-9 diagnoses for CVD in a primary care setting. When patients have CVD complications, they are often hospitalized and/or referred to cardiologists, who make the diagnosis. It is possible that notes from other providers are not recorded in the primary care providers' medical record, which could lead to under-diagnosis. Similarly, atherosclerosis is a 'silent' disease state, which typically goes undiagnosed until a symptomatic event has occurred. Another limitation was variation in the number of $HbA1_C$ values available for each patient with some patients having only two (one in each calendar year) and others having up to four or more values in a calendar year. The mean follow-up period was 1.8 years, which probably did

not allow time for long-term accumulation of vascular damage. This, in addition to lack of documentation and under-diagnosis, could have led to low incidence rates in this study. With any EMR study, the data are only as accurate as the coding. Specific medications and medication taking behaviors (e.g., prescription claims) were not included. This information may have helped understand patient disease severity as well as medication adherence. Finally, there were other risk factors that were not accounted for because of the subjective nature or lack of reliability in reporting and documentation. These include duration of diabetes, alcohol intake, diet and physical activity.

4.5 Conclusions and Future Research

This study of T2DM patients which adjusted for multiple cardiovascular risk factors did not find a significant association between incident CA or ACS and mean serial $HbA1_C$ ($HbA1_C \geq 7\%$ compared to $<7\%$) over a mean follow-up of approximately two years. This observed lack of benefit may be due to other interventions leading to decreased cardiovascular risk that was not adjusted for in this study including HDL-C, blood pressure changes, weight changes and the use of ACE inhibitors. Future studies should consider using larger sample size and longer treatment duration to identify the specific modifiable cardiovascular risk factors including those not adjusted for in this study that could be targeted in the same population cohort used in the study. Also, more detailed information on adherence and persistence to relevant pharmacotherapy (diabetes, hypertension, dyslipidemia) should be pursued.

References

1. *National Diabetes Fact Sheet, 2007*.
2. *Centers for Disease Control and Prevention. National diabetes fact sheet: general information and national estimates on diabetes in the United States, 2007. Atlanta, GA: U.S. Department of Healthand Human Services, Centers for Disease Control and Prevention, 2008. Available at: http://apps.nccd.cdc.gov/DDTSTRS/FactSheet.aspx Accessed: January 31, 2010*.
3. Grundy, S.M., B. IJ, B. GL, et al., *Diabetes and Cardiovascular Disease : A Statement for Healthcare Professionals From the American Heart Association.* Circulation, 1999. **100**(10): p. 1134-1146.
4. Braunwald, E., A. EM, J. Beasley, et al., *ACC/AHA Guidelines for the Management of Patients With Unstable Angina and Non±ST-Segment Elevation Myocardial Infarction A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Unstable Angina)*. J Am Coll Cardiol, 2000. **36**: p. 970-1062.
5. Sobel, B.E. and D. Schneider, *Cardiovascular Complications in Diabetes Mellitus.* Current Opinion in Pharmacology, 2005. **5**: p. 143-148.
6. Golden, S.H., E. Selvin, and K. Cunningham, *Glycaemic Status and Cardiovascular Disease in Type 2 Diabetes Mellitus: Re-visiting Glycated Haemoglobin Targets for Cardiovascular Disease Prevention.* Diabetes, Obesity and Metabolism, 2007. **9**: p. 792-798.
7. Haffner, S.M., S. Lehto, T. Önnemaa, K. Pyorala, and M. Laakso, *Mortality From Coronary Heart Disease In Subjects With Type 2 Diabetes and In Nondiabetic Subjects With and Without Prior Myocardial Infarction.* N Engl J Med, 1998. **339**: p. 229-34.
8. Malmberg, K., S. Yusuf, H. Gerstein, et al., *Impact of Diabetes on Long-Term Prognosis in Patients With Unstable Angina and Non-Q-Wave Myocardial Infarction Results of the OASIS (Organization to Assess Strategies for Ischemic Syndromes) Registry.* Circulation, 2000. **102**: p. 1014-1019.
9. National Cholesterol Education Program, *Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). NIH Pub. No. 02-5125. Bethesda, MD: National Heart, Lung, and Blood Institute, 2002;284 pages. Available at http://www.nhlbi.nih.gov/guidelines/ cholesterol/index.htm. Accessed February 2, 2010*.
10. Donaghue, K.C., *Microvascular and Macrovascular Complications Associated with Diabetes in Children and Adolescents.* Pediatric Diabetes 2009. **10**: p. 195-203.
11. Fox, C.S., S. Coady, P.D. Sorlie, et al., *Increasing Cardiovascular Disease Burden Due to Diabetes Mellitus: The Framingham Heart Study.* Circulation, 2007. **115**: p. 1544-1550.

12. Fowler, M.J., *Microvascular and Macrovascular Complications of Diabetes.* Clinical Diabetes, 2008. **26**: p. 77-82.
13. *Centers for Disease Control and Prevention. National diabetes surveillance system. Diabetes data & trends. Available at http://www.cdc.gov/diabetes/statistics/index.htm. Accessed January 21, 2010.*
14. American Diabetes Association, *Standards of Medical Care in Diabetes—2010.* Diabetes Care, 2010. **33**(Suppl 1): p. S1-S61.
15. The United States Renal Data System, *USRDS Annual Data Report. Bethesda, National Institutes of Health. National Institute of Diabetes and Digestive and Kidney Diseases*. 2009. Accessed April 20, 2010.
16. Rahman, S., T. Rahman, A. Ismail, and A. Rashid, *Diabetes-Associated Macrovasculopathy: Pathophysiology and Pathogenesis.* Diabetes, Obesity and Metabolism, 2007. **9**: p. 767–780.
17. Gaede, P., P. Vedel, N. Larsen, et al., *Multifactorial Intervention and Cardiovascular Disease in Patients with Type 2 Diabetes.* N Engl J Med, 2003. **348**(5): p. 383-393.
18. Remuzzi, G., A. Schieppat, and P. Ruggenenti, *Nephropathy In Patients With Type 2 Diabetes.* N Engl J Med, 2002. **346**(15): p. 1145-1151.
19. Brown, W.V., *Microvascular Complications of Diabetes Mellitus: Renal Protection Accompanies Cardiovascular Protection.* Am J Cardiol, 2008. **102**: p. 10S-13S.
20. Klausen, K., K. Borch-Johnsen, B. Feldt-Rasmussen, et al., *Very Low Levels of Microalbuminuria Are Associated With Increased Risk of Coronary Heart Disease and Death Independently of Renal Function, Hypertension, and Diabetes.* Circulation, 2004. **110**: p. 32-35.
21. Vinik, A.I., E.S. Strotmeyer, A.A. Nakave, and C.V. Patel, *Diabetic Neuropathy in Older Adults.* Clin Geriatr Med, 2008. **24**(3): p. 407-v.
22. Zochodne, D.W., *Diabetic Polyneuropathy: An Update.* Current Opinion in Neurology 2008. **21**(5): p. 527-533.
23. Shah, C.A., *Diabetic Retinopathy: A Comprehensive Review.* Indian Journal of Medical Sciences 2008. **68**(12): p. 500-519.
24. Kumar, A. and C.P. Christopher, *Acute Coronary Syndromes: Diagnosis and Management, Part I.* Mayo Clin Proc, 2009. **84**(10): p. 917-938.
25. Hurst, R.T. and R.W. Lee, *Increased Incidence of Coronary Atherosclerosis in Type 2 Diabetes Mellitus: Mechanisms and Management.* Ann Intern Med, 2003. **139**(10): p. 824-34.
26. Williams, S.B., J. Cusco, M. Roddy, J. MT, and M. Creager, *Impaired Nitric Oxide-Mediated Vasodilation in Patients With Non-Insulin-Dependent Diabetes Mellitus.* J Am Coll Cardiol, 1996: p. 567-574.
27. Osende, J.I., J. Badimon, V. Fuster, et al., *Blood Thrombogenicity in Type 2 Diabetes Mellitus Patients Is Associated With Glycemic Control.* J Am Coll Cardiol, 2001. **38**(5): p. 1307-1312.

28. Shechter, M., C. Merz, M. Paul-Labrador, and S. Kaul, *Blood Glucose and Platelet-Dependent Thrombosis in Patients With Coronary Artery Disease.* J Am Coll Cardiol, 2000. **35**(2): p. 300-307.
29. Thögersen, A.M., J. Jansson, K. Boman, et al., *High Plasminogen Activator Inhibitor and Tissue Plasminogen Activator Levels in Plasma Precede a First Acute Myocardial Infarction in Both Men and Women: Evidence for the Fibrinolytic System as an Independent Primary Risk Factor.* Circulation, 1998 **98**: p. 2241-2247.
30. Williams, S.B., A. Goldfine, F. Timimi, et al., *Acute Hyperglycemia Attenuates Endothelium-Dependent Vasodilation in Humans In Vivo.* Circulation, 1998. **97**: p. 1695-1701.
31. Despres, J.-P., B. Lamarche, P. Mauriege, et al., *Hyperinsulinemia As An Independent Risk Factor For Ischemic Heart Disease.* N Engl J Med, 1996. **334**: p. 952-957.
32. Guzik, T.J., S. Mussa, D. Gastaldi, et al., *Mechanisms of Increased Vascular Superoxide Production in Human Diabetes Mellitus: Role of NAD(P)H Oxidase and Endothelial Nitric Oxide Synthase.* Circulation, 2002. **105**: p. 1656-1662.
33. Jeppesen, J., H. Hein, P. Suadicani, and F. Gyntelberg, *Relation of High TG–Low HDL Cholesterol and LDL Cholesterol to the Incidence of Ischemic Heart Disease : An 8-Year Follow-up in the Copenhagen Male Study* Arteriosclerosis, Thrombosis, and Vascular Biology, 1997. **17**: p. 1114-1120.
34. Stienberg, H.O., M. Tarshoby, R. Monestel, et al., *Elevated Circulating Free Fatty Acid Levels Impair Endothelin-Dependent Vasodilation.* J Clin Invest, 1997. **100**: p. 1230-1239.
35. Hansson, G.K., *Inflammation, Atherosclerosis, and Coronary Artery Disease.* new England Journal of Medicine, 2005. **352**: p. 1685-95.
36. Devine, P.J., D.W. Carlson, and A.J. Taylor, *Clinical Value of Carotid Intima-Media Thickness Testing.* J Nucl Cardiol, 2006. **13**(5): p. 710-8.
37. Larsen, J.R., M. Brekke, L. Bergengen, et al., *Mean HbA_{1C} Over 18 Years Predicts Carotid Intima Media Thickness in Women With Type 1 Diabetes.* Diabetologia, 2005. **48**: p. 776-779.
38. Beckman, J.A., M.A. Creager, and P. Libby, *Diabetes and Atherosclerosis: Epidemiology, Pathophysiology, and Management.* JAMA, 2002. **287**(19): p. 2570-81.
39. American Association of Clinical Endocrinologists (AACE) Diabetes Mellitus Clinical Practice Guidelines Task Force, *American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the Management of Diabetes Mellitus.* Endocr Pract. , 2007. **13**(Suppl 1): p. 1-66.
40. American Diabetes Association (ADA), *Executive Summary: Standards of Medical Care in Diabetes—2010.* Diabetes Care, 2010. **33**: p. S1-S10.
41. Nathan, D.M., J. Kuenen, R. Borg, et al., *Translating the A1C Assay to Estimated Average Glucose Values.* Diabetes Care, 2008. **31**: p. 1473-1478.

42. The International Expert Committee, *International Expert Committee Report on the Role of $A1_C$ Assay in the Diagnosis of Diabetes.* Diabetes Care, 2009. **32**: p. 1372-1334.
43. Temelkova-Kurktschiev, T., Koehler C, Schaper F, et al., *Relationship Between Fasting Plasma Glucose, Atherosclerosis Risk Factors and carotid Intima Media Thickness in Non-Diabetic Individuals.* Diabetologia, 1998. **41**: p. 706-712.
44. Adams, R.J., S.L. Appleton, C.L. Hill, et al., *Independent Association of HbA_{1c} and Incident Cardiovascular Disease in People Without Diabetes.* Obesity, 2009. **17**(3): p. 559-563.
45. Hoogwerf, B.J., D.L. Sprecher, G.L. Pearce, et al., *Blood Glucose Concentrations <125 mg/dl and Coronary Heart Disease Risk.* The American Journal of Cardiology, 2002. **89**: p. 596-598.
46. Roger, V.L., T. Goraya, C. Leibson, et al., *Coronary Atherosclerosis in Diabetes Mellitus: A Population-Based Autopsy Study.* Journal of the American College of Cardiology, 2002. **40**(5): p. 946-953.
47. The Diabetes Control and Complications Trial Research Group, *The Effect of Intensive Treatment of Diabetes on the Development and Progression of Long-Term Complications in Insulin-Dependent Diabetes Mellitus.* N Engl J Med, 1993. **329**: p. 977-986.
48. UK Prospective Diabetes Study (UKPDS) Group, *Intensive Blood-Glucose Control with Sulphonylureas or Insulin Compared With Conventional Treatment and Risk of Complications in Patients with Type 2 Diabetes (UKPDS 33).* Lancet, 1998. **352**: p. 837-853.
49. The ADVANCE Collaborative Group, *Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes.* N Engl J Med, 2008. **358**: p. 2560-2572.
50. Goff, D.C., H. Gerstein, H. Ginsberg, et al., *Prevention of Cardiovascular Disease in Persons with Type 2 Diabetes Mellitus: Current Knowledge and Rationale for the Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial.* Am J Cardiol, 2007. **99**: p. [suppl]:4i-20i.
51. Leither, L.A. and A. Cheng, *Diabetes and Cardiovascular Disease: The Role of Glycemic Control.* Current Diabetes Reports 2009. **9**: p. 65-72.
52. Selvin, E., S. Marinopoulos, G. Berkenblit, et al., *Meta-Analysis: Glycosylated Hemoglobin and Cardiovascular Disease in Diabetes Mellitus.* Ann Intern Med, 2004. **141**: p. 421-423.
53. Duckworth, W., C. Abraira, T. Moritz, et al., *Glucose Control and Vascular Complications in Veterans with Type 2 DM.* N Engl J Med, 2009. **360**: p. 129-139.
54. The Action to Control Cardiovascular Risk in Diabetes Study Group, *Effects of Intensive Glucose Lowering in Type 2 Diabetes.* N Engl J Med, 2008. **358**: p. 2545-2559.
55. Selvin, E., Coresh J, Golden SH, et al., *Glycemic Control and Coronary Heart Disease Risk in Persons With and Without Diabetes.* Arch Intern Med, 2005. **165**: p. 1910-1916.

56. Ballantyne, C.M. and L.S. Clair, *Biological Surrogates For Enhancing Cardiovascular Risk Prediction in Type 2 Diabetes Mellitus.* Am J Cardiol, 2007. **99[suppl]**(4A): p. 80B-88B.
57. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group, *Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes.* N Engl J Med, 2005. **353**: p. 2643-2653.
58. Holman, R.R., S.K. Paul, M. Bethel, D.R. Matthews, and A.W. Neil, *10-Year Follow-up of Intensive Glucose Control in Type 2 Diabetes.* New England Journal of Medicine, 2008. **359**(15): p. 1577-1589.
59. *CommUnityCare*. Available from: http://communitycaretx.org/about_us.html Accessed June 19, 2010.
60. Strom, B.L. and S.E. Kimmel, *Textbook of Pharmacoepidemiology*, in *Sample Size Considerations for Pharmacoepidemiology*, B.L. Strom, Editor. 2007, John Wiley & Sons, Ltd.
61. Avogadro, A., C. Giorda, M. Maggini, et al., *Incidence of Coronary Heart Disease in Type 2 Diabetic Men and Women.* Diabetes Care, 2007. **30**: p. 1241-1247.
62. Saito, I., A.R. Folsom, F.L. Brancati, et al., *Nontraditional Risk Factors for Coronaory Heart Disease Incidence among Persons with Diabetes: The Atherosclerosis Risk in Communities (ARIC) Study.* Ann Intern Med, 2000. **133**: p. 81-91.
63. Fox, C.S., M.J. Pencina, P.W.F. Wilson, et al., *Lifetime Risk of Cardiovascular Disease Among Individuals With and Without Diabetes Stratified by Obesity Status in the Framingham Heart Study.* Diabetes Care, 2008. **31**: p. 1582-1584.
64. Stratton, I.M., A. Adler, H. Neil, et al., *Association of Glycaemia With Macrovascular and Microvascular Complications of Type 2 Diabetes (UKPDS 35): Prospective Observational Study.* BMJ, 2000. **321**: p. 405-412.
65. Gaede, P., L. Lund-Andersen, H.-H. Parving, and O. Pedersen, *Effect of a Multifactorial Intervention on Mortality in Type 2 Diabetes.* N Engl J Med, 2008. **358**: p. 580-91.
66. Bild, D.E., D.A. Bluemke, R.D. Burke, et al., *Multi-Ethnic Study of Atherosclerosis: Objective and Design.* Am J Epidemiol, 2002. **156**: p. 871-881.

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