QUALITY OF DIABETES CARE IN A US MANUFACTURING COHORT: A COMPARISON OF QUALITY INDICATORS AS PREDICTORS OF DIABETES COMPLICATIONS

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Abstract

This study examines three process measures of diabetic care and their association with four complications of diabetes - Coronary Artery Disease (CAD), Heart Failure (HF), Stroke and Renal Disease (RD) - in a cohort comprised of hourly and salaried employees of a single large manufacturing company at geographically diverse regions in the United States. Quality of care was measured by adherence to consensus standards for A1C and lipid testing and screening for microalbuminuria. A retrospective cohort study was conducted from January 1, 2003 to December 31, 2009 of 1,797 diabetic employees of a US manufacturer who were enrolled in the same health insurance plan. Diabetics who received all three QOCM in the baseline year were compared to diabetics who received less than three QOCM in the baseline year and were analyzed to address their association with the four complications.

Cox proportional hazard regression models were used to assess potential associations between diabetes QOCM and time to complication. Potential confounding risk factors included sex, age, ethnicity, income, marital status, education, smoking, diabetes severity and health comorbidity risk scores.

The overall health benefits for diabetics who received all three QOCM at baseline were noteworthy; they experienced reduced risk for HF (HR 0.39, CI [.19 - .81], p = 0.0117) and RD

(HR 0.48, CI [.24 - .95] p = 0.0339) compared to the people who received less than three QOCM. Results suggest that diabetics who received all three QOCM experienced lower complications and is associated with reduced complication risk - regardless of access to care and other factors. These results suggest that any improvement in screening is likely to reduce the risk of diabetes complications. This study contributes to the literature by examining adherence to recommended processes of care and patient complications together. The public health implications of this study can be used to inform the design or revision of disease management programs and process of care measures.

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PREFACE

I wish to thank all the members of my committee for their support and encouragement. I also thank all of my colleagues at Yale, Alcoa and Stanford for their encouragement, and most importantly their friendship. Finally, I wish to thank my daughter, Cristina, for giving me the energy to return to school and my husband, David, for being my greatest champion.

1.0 INTRODUCTION

Diabetes presents a significant public health burden that leads to increased morbidity, mortality, and economic costs (Saydah, Fradkin, & Cowie, 2004). In 2010, the estimated prevalence of diabetes among persons aged 18 years or older ranged from five to 13% in the United States and its territories (Chowdhury et al., 2010). Diabetes can cause debilitating physical complications, including cardiovascular disease (Centers for Disease Control and Prevention, 2010; Grundy et al., 1999; Haffner, Lehto, Rönnemaa, Pyörälä, & Laakso, 1998), heart failure (Boudina & Abel, 2007), stroke (Feskens & Kromhout, 1992; Herlitz, Karlson, Lindqvist, & Sjolin, 1998; Kissela et al., 2005; Kuusisto, Mykkanen, Pyorala, & Laakso, 1994; Rodbard et al., 2007), renal disease (Gross et al., 2005; Levin & Rocco, 2007; Perneger, Brancati, Whelton, & Klag, 1994), hypertension (Rodbard et al., 2007; Sowers, Epstein, & Frohlich, 2001) and visual impairment (Klein, Klein, Moss, Davis, & DeMets, 1984; Singh, Armstrong, & Lipsky, 2005; Zhang et al., 2006), among others. Diabetes often develops nine to 12 years before it is diagnosed (Lillioja et al., 1993). More than 50% of patients diagnosed with T2DM have at least one complication at the time of diagnosis that could have been prevented (Rodbard et al., 2007).

On average, medical expenditures for people with diagnosed diabetes are more than double those of the non-diabetic population. Approximately one out of every five health care dollars in the US is spent caring for someone with diagnosed diabetes, which in 2007 totaled $174 billion, including $116 billion in excess medical expenditures and $58 billion in reduced

national productivity (Petersen, 2008). An additional $58 billion was spent that same year treating microvascular and macrovascular complications of diabetes, including myocardial infarction, stroke, renal disease, retinopathy and neuropathy, along with $31 billon in excess general medical costs (Petersen, 2008).

In addition to medical complications and the related physical and financial burdens they cause, diabetes impacts lives in many other ways. Approximately 11 to 15% of patients with Type 2 diabetes (T2DM) also suffer from major depression (Katon et al., 2005). Diabetes also has a financial cost in the form of increased absenteeism ($2.6 billion), reduced work productivity for the employed population ($20.0 billion), reduced productivity for those not in the labor force ($0.8 billion), unemployment due to disease-related disability ($7.9 billion), and lost productive capacity due to early mortality ($26.9 billion). Compared to individuals without diabetes, men and women with diabetes are 5.4% and 6% more likely to have work limitations, respectively. Diabetes affects patients, employers, and society at large, not only by reducing employment but also by contributing to work loss and health-related work limitations for those who remain employed (Petersen, 2008; Tunceli et al., 2005).

Fortunately, a significant body of research from large randomized controlled trials has clearly established that several effective treatments and practices provide evidence that intensive treatment of diabetes mellitus and conditions known to be risk factors can significantly decrease the development and/or progression of chronic complications (DCCT, 1993, 1996; EDIC, 1999; ETDRS, 1991; Goldberg et al., 1998; Knowler et al., 2002; Litzelman et al., 1993; Mann, 2000; Ohkubo et al., 1995; Rodbard et al., 2007; Stratton et al., 2000; UKPDS 33, 1998; UKPDS 38, 1998; UKPDS 40, 1998). Specific benefits are derived by monitoring and controlling glycemia,

blood pressure and lipids, screening for microalbuminuria and retinopathy, and conducting routine foot examinations (Saaddine et al., 2006).

For most of the 20th century, diabetes care was suboptimal and varied in the United States (Beckles et al., 1998; Engelgau et al., 1998; Fleming et al., 2001; Kenny, Smith, Goldschmid, Newman, & Herman, 1993; Saaddine et al., 2006). It was recognized that a national consensus on process measures could enhance the delivery of care and provide a method for assessing care within and across health care settings while providing a meaningful mechanism for quality improvement. Founded in 1997, the National Diabetes Quality Improvement Project developed a comprehensive set of process and intermediate outcome measures to assess quality of care for diabetes patients that are now considered standard (Fleming et al., 2001). The measures were developed based on the theory that if diabetics and their physicians adhere to the process and intermediate outcome measures they will have fewer complications (Fleming et al., 2001). The process measures include annual screenings for lipids and microalbuminuria and at least two measurements of A1C (a measure of blood glucose levels over the preceding three months), as well as annual flu vaccinations, dilated eye exams and biannual foot examinations (American Diabetes Association, 2005). The American Diabetes Association Provider Recognition Program, the American Medical Association Diabetes Measures Group, the Veterans Administration's performance monitoring program, the National Committee for Quality Assurance (NCQA) and other national consensus standards and the Health Plan Employer Data and Information Set (HEDIS) include these process measures as part of their performance monitoring programs.

A number of studies (Beckles et al., 1998; Fleming et al., 2001; Grant, Buse, & Meigs, 2005; Imperatore et al., 2004; Jencks, Huff, & Cuerdon, 2003; Kenny et al., 1993; Koro, Bowlin,

Bourgeois, & Fedder, 2004; Mangione et al., 2006; McClain, Wennberg, Sherwin, Steinmann, & Rice, 2003; Rodbard et al., 2007; Roubideaux et al., 2004; Saaddine et al., 2006; Saaddine et al., 2002; Sawin, Walder, Bross, & Pogach, 2004; Saydah et al., 2004; Selby et al., 2007) have used these performance measures to assess and document improvement in the care provided to patients with diabetes at the health system, provider and health plan levels. These studies provide evidence of the substantial gaps between national performance measures for diabetes care (e.g., frequent A1C testing, screenings for diabetic retinopathy, cholesterol testing, routine foot exams, etc.) and actual care received by diabetics in the United States. For instance, using three performance indicators from the NCQA and HEDIS guidelines, one research study (Jencks et al., 2003) found that the percentage of Medicare patients receiving appropriate diabetes related preventative care services in 1998 and 1999 in the median state was just 71% for A1C, 69% for eye exams and 57% for cholesterol testing. A follow up study of the same cohort in 2000 and 2001 indicated that care had improved substantially for the same medical conditions to 78%, 70%, and 74%, respectively (Jencks et al., 2003).

Optimal diabetes care depends on healthcare providers adhering to evidence-based practice guidelines in the delivery of care, and patients adhering to self-management recommendations in order to maximize intermediate outcomes and reduce complications (Ward et al., 2004). Process measures assess the degree to which providers follow the evidence-based practice guidelines (e.g., the percentage of patients with two A1C tests in a year, at least one lipid test in a year, at least one screen for microalbuminuria in a year, etc.). Intermediate outcome measures assess the extent of glycemic, lipid, and blood pressure control in patients with diabetes (e.g., the percentage of patients with a measured A1C < 7% and a measured low-risk lipid cholesterol (LDL) value ≤ 100 mg/dl). Process and outcome measures are distinct and

complementary aspects assessing quality of diabetes care, and the relationship between processes of care and patient outcomes, specifically, complications, are a central issue in health services research.

Although it has not been firmly established that early detection of T2DM and intervention actually improves long-term outcomes, several studies provide evidence that adherence to consensus standards is associated with reduced complications. The results of both UKPDS studies and the DCCT are consistent: intensive glycemic monitoring and control significantly reduces microvascular complications (DCCT, 1993, 1996; DCCT/EDIC, 2000; Duckworth et al., 2009; Margetts, 1995; Nathan et al., 2005; Nathan et al., 2009; Phillips & Molitch, 1995; UKPDS 33, 1998). Other meta analyses also have demonstrated a reduction in the risk of heart disease with intensive decreases in blood glucose versus standard treatment (Kelly et al., 2009; Klein, 1995; Nathan et al., 2005; Ray et al., 2009; Stratton et al., 2000). Additionally, achieving high metabolic control (A1C $<$ 7%), treating hypertension ($<$ 130/80 mm Hg or $<$ 125/75 mm Hg if proteinuria $>$ 1.0 g/24 h and increased serum creatinine), using drugs with blockade effects on the renin-angiotensin-aldosterone system, and treating dyslipidemia (LDL cholesterol $<$ 100 mg/dl) are effective in preventing the development of microalbuminuria, delaying the progression to more advanced stages of nephropathy, and reducing cardiovascular mortality in patients with T1DM and T2DM (Gross et al., 2005; Levin & Rocco, 2007). The results of multiple large randomized controlled trials also indicate that blood pressure control reduces morbidity and mortality among diabetics (Adler et al., 2000; Gross et al., 2005; Newman et al., 2005; Saydah et al., 2004; UKPDS 33, 1998; UKPDS 38, 1998). Proper screening (e.g., dilated fundus examination), glycemic and hypertension control, and early interventions incorporating both surgical and pharmacologic therapies also can help

diabetics avoid severe vision loss associated with diabetic retinopathy (Mohamed, Gillies, & Wong, 2007).

Computer simulation models of T2DM of subjects over age 25 suggest that the cost increases associated with screening and early treatment may be worth it (Engelgau et al., 1998). However, it is important to note that the benefits of early detection in the model were derived more from postponement of complications from diabetes than from additional life-years. In other analyses, screening for impaired glucose tolerance and undiagnosed T2DM followed by intervention was more cost effective than no screening at all (Gillies et al., 2008).

1.1 ACCESS TO CARE AND SES

It is unknown whether improvements in adherence to national consensus standards for diabetes have benefited all groups equally, or whether, as noted in earlier studies (Karter et al., 2002), socioeconomic differences that lead to substandard health care for minorities remain. The availability of health insurance is a strong factor associated with better process and outcome measures (Saaddine et al., 2002). However, reasonable access to health care depends on many factors, including the availability of health services in a community and personal care-seeking behavior. These and other factors are often trumped by whether a person can afford the costs of needed care. Health services research shows a strong association between health insurance coverage and access to primary and preventive care, the treatment of acute and traumatic conditions, and the medical management of chronic illnesses such as diabetes (Hoffman & Paradise, 2008). The same research connects being uninsured or underinsured with adverse health outcomes, including declines in health and functioning, the existence of preventable health

problems, severe disease at the time of diagnosis, and premature mortality (Hoffman & Paradise, 2008; Institute of Medicine, 2002). Although health insurance alone would neither eliminate disparities in access to health care nor equalize health across subgroups of Americans, having health insurance is clearly connected to a longer life of better quality (Institute of Medicine, 2002).

Disparate access to quality health care is a common explanation for socioeconomic and ethnic disparities in diabetic complication rates within the US population (Selby et al., 2007; Smedley, Stith, & Nelson, 2002). Population-based studies suggest that racial and ethnic minorities and people of lower socioeconomic status (SES) experience worse long term diabetes outcomes than whites and people of higher SES (Brown et al., 2005). Other studies have shown less adherence to processes of diabetes care (dilated retinopathy, etc.) and worse intermediate outcomes among racial and ethnic minorities and individuals with lower incomes or education levels (Karter et al., 2002; Lanting, Joung, Mackenbach, Lamberts, & Bootsma, 2005). Since racial and ethnic minorities and poorer people with diabetes are less adequately insured than whites or people higher on the SES ladder (Brown et al., 2005), differential access to care may contribute to these observations. Research from managed care settings (Karter et al., 2002; Martin, Selby, & Zhang, 1995) and the Veterans Health Administration (Heisler, Smith, Hayward, Krein, & Kerr, 2003; Young, Maynard, & Boyko, 2003) suggest that racial and ethnic disparities in diabetes processes and outcomes may be reduced in settings offering more uniform access to care. In the TRIAD research, 7,456 adults who were enrolled in health plans participated in a six center cohort study on diabetes treatment and outcomes in a managed care setting; minority race and ethnicity were consistently associated with worse processes or outcomes (Brown et al., 2005). Access to care and associated variables such as SES and

ethnicity are frequent confounders in research studies examining the relationship between quality of diabetes care and intermediate outcomes and complications using participant samples from the general population.

1.2 RESEARCH JUSTIFICATION

Changing demographics in the US population will only fuel the diabetes epidemic, and many more people will be stricken with the disease in the years to come (Centers for Disease Control and Prevention, 2008). Ensuring access to and delivery of high-quality care for all people with diabetes should be a national priority, as it has serious financial and social implications. Understanding how to better implement existing diabetes care interventions with minimal resources will be critical to ensuring the highest possible quality of life for millions of Americans afflicted with the disease.

Healthy People 2010, a document created by the US Department of Health and Human Services, highlights wide gaps between public health performance and actual outcomes based on many quality indicators (Jencks et al., 2003; US Department of Health and Human Services, 2010). Despite advances in diabetes research and consensus recommendations for diabetes care, adherence to patient care processes and health outcomes are still falling short of targeted levels (Saaddine et al., 2006; Saaddine et al., 2002). Furthermore, even people with apparently good access to health services receive care that falls far short of what it could be (Jencks et al., 2003). As previously stated, there is data suggesting a relationship between health outcomes in diabetics and quality of care received (Saaddine et al., 2002, (Hoffman & Paradise, 2008; Brown et al., 2005; Martin, Selby, & Zhang, 1995) However these results are confounded by factors such as

social and access differences between groups. Therefore, it is not entirely clear if the quality of care received is the primary factor that improves the outcome in diabetics or the good socioeconomic circumstances such as income, education, ethnicity and other social factors that allows good care to occur.

This study examines three process measures of diabetic care and their association with four complications of diabetes - Coronary Artery Disease (CAD), Heart Failure (HF), Stroke and Renal Disease (RD) - in a cohort comprised of hourly and salaried employees of a single large manufacturing company at geographically diverse regions in the United States. This cohort provides a unique opportunity to answer the study question because of the ethnic diversity of the population, the uniform health care benefits offered by the employer and the comparable access to healthcare by the workers. Processes of care will be measured by adherence to consensus standards for A1C and lipid testing and screening for microalbuminuria. Most of the diabetes care literature focuses on adherence to patient care processes (e.g., frequency of A1C testing, lipid testing, vision screening, etc.) and intermediate outcomes such as the actual levels of A1C testing, results of lipid tests and actual blood measurements.; very few evaluate adherence and actual outcomes and complications (Renders et al., 2001). Because of the unique database and the study design, actual outcomes of diabetic complications (CAD, HF, Stroke and RD), and not intermediate outcomes of care will be evaluated in this analysis. This is important because of the ability of this study to separate out the care processes from other explanations of why the people who got good care did better.

The employer's electronic administrative data for personnel, financial and health insurance will be used to obtain sex, age, ethnicity, income and marital status minimizing the potential confounding associated with SES covariates. The study setting will reduce the

potential for random effects by evaluating the quality of care delivered through the same provider networks within the employment context and minimize confounding associated with access to care. Studying a geographically and ethnically diverse population of diabetics employed by a US manufacturer with the same insurance is a highly advantageous study setting for analyzing associations of quality of healthcare and disease outcomes (Einav, Finkelstein, & Cullen, 2010; Einav, Finkelstein, Pascu, & Cullen, Under Review; Einav, Finkelstein, Ryan, Schrimpf, & Cullen).

Measuring quality of care processes and complications in isolation yields incomplete results and ignores important implications for diabetes care; the two should not be separated. This study contributes to the literature by examining adherence to recommended processes of care and patient complications *together* and by providing insights into why some diabetics are not yet benefiting fully from quality improvement efforts (Jencks et al., 2003; US Department of Health and Human Services, 2010). In this way, the results of this study can be used to inform the design or revision of disease management programs and process of care measures.

2.0 LITERATURE REVIEW

2.1 PREVALENCE OF DIABETES

In 2008, the Centers for Disease Control and Prevention (CDC) reported that 1.6 million Americans aged 20 years or older are diagnosed with diabetes each year (Centers for Disease Control and Prevention, 2008). Currently, diabetes is the seventh leading cause of death, affecting nearly 24 million people in the United States (Centers for Disease Control and Prevention, 2008, 2011). "As the worldwide diabetes epidemic continues to unfold, some experts have asked whether the war against it is being lost" (Fleming et al., 2001).

Based on a CDC analysis of the National Health Interview Survey, the number of adults in the United States with diagnosed diabetes has increased by 61% since 1991, and is projected to more than double by 2050 (Centers for Disease Control and Prevention, 2011). The CDC report predicts that the number of new diabetes cases each year will increase from 8 per 1,000 people in 2008, to 15 per 1,000 in 2050. These projected increases are largely attributable to the aging US population, an increasing number of people from higher risk ethnic origins, and the fact that people with diabetes are living longer (Boyle et al., 2001). If current trends continue, those with diabetes will lose an average of 10 to 15 life-years (Narayan, Boyle, Thompson, Sorensen, & Williamson, 2003; Saaddine et al., 2006). Similarly, if diabetes mortality rates remain relatively low, diabetes prevalence in the United States will increase to 33% by 2050

(Centers for Disease Control and Prevention, 2010). Therefore, effective strategies must be created to buffer the financial and societal impact of diabetes on the nation.

Given the large number of Americans with undiagnosed diabetes mellitus, early detection and treatment is imperative to addressing the diabetes epidemic (Centers for Disease Control and Prevention, 2011; Rodbard et al., 2007). In 1997, the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus issued new diagnostic and classification criteria (Gavin et al., 1997), and in 2003, modifications were made regarding the diagnosis of impaired fasting glucose (Genuth et al., 2003). Today, diabetes is classified into four clinical types:

1. Type 1 diabetes mellitus (T1DM), resulting from cell destruction and usually leading to absolute insulin deficiency;
2. Type 2 diabetes mellitus (T2DM), resulting from a progressive insulin secretion defect coupled with insulin resistance;
3. Gestational diabetes mellitus, diagnosed in women during pregnancy; and
4. Specific types of diabetes due to other causes (e.g., genetic defects in cell function, genetic defects in insulin action, diseases of the pancreas, and induced by drugs or chemicals) (American Diabetes Association, 2005, 2010).

Approximately 90 to 95% of all diabetes diagnoses in the United States are T2DM (Rodbard et al., 2007), and the disease often develops nine to 12 years before it is diagnosed (Lillioja et al., 1993). T2DM is caused by a combination of complex metabolic disorders that result from coexisting defects of multiple organs, including insulin resistance in muscle and adipose tissue, a progressive decline in pancreatic insulin secretion, unrestrained hepatic glucose production and other hormonal deficiencies (Aronoff, Berkowitz, Shreiner, & Want, 2004; Ferrannini, 1998; Lillioja et al., 1993). T2DM occurs more frequently in women with a history

of gestational diabetes and in individuals with hypertension or dyslipidemia. Diabetes is also associated with a strong genetic predisposition. Almost all other cases (five to 10%) are T1DM, with gestational diabetes or diabetes from other causes accounting for just a fraction of diagnoses (Rodbard et al., 2007). Some patients cannot be clearly classified as having T1DM or T2DM even though the clinical presentations and disease progressions vary considerably (American Diabetes Association, 2010; Rodbard et al., 2007). In many cases, the true diagnosis may emerge only over time.

2.2 DIABETES COMPLICATIONS

Diabetes is associated with a high prevalence of comorbidities (Katon et al., 2005). Several risk factors, including obesity, a sedentary lifestyle, genetic predisposition, ethnicity and advanced age increase the risk of developing diabetes; when coupled with conditions such as hypertension and dyslipidemia, they exacerbate the potential for related macrovascular and microvascular complications (Adler et al., 2000; Bakris et al., 2000; Coutinho, Gerstein, Wang, & Yusuf, 1999; Fong et al., 2004; Fox, Sullivan, D'Agostino, & Wilson, 2004; Frank, 2004; Gerstein et al., 2007; Gross et al., 2005; Haffner, Lehto, Rönnemaa, Pyörälä, & Laakso, 1998; Khaw et al., 2001; Klein, Barrett-Connor, Blunt, & Wingard, 1991; Miettinen et al., 1998; Perneger, Brancati, Whelton, & Klag, 1994; Phillips & Molitch, 1995; Ray et al., 2009; Rodbard et al., 2007; Selvin et al., 2004; Stratton et al., 2000; Tuomilehto, 2003; UKPDS 33, 1998; UKPDS 38, 1998; Vinik, Maser, Mitchell, & Freeman, 2003). Macrovascular complications include: coronary artery disease, which can lead to myocardial infarction; cerebral vascular disease, which can lead to strokes; and peripheral vascular disease. Microvascular complications include nephropathy or

renal disease (disease of the kidney), which can require dialysis and lead to kidney failure; retinopathy (disease of the retina), which can lead to blindness; and neuropathy (disease of the nerves), which can lead to foot ulcerations and amputation (Lillioja et al., 1993).

Many of these complications produce no symptoms in the early stages, and more than 50% of patients diagnosed with T2DM have at least one complication at the time of diagnosis that could have been prevented (Rodbard et al., 2007). Approximately 20% of newly diagnosed T2DM patients have diabetic retinopathy (Harris, Klein, Welborn, & Knuiman, 1992), 10% have nephropathy (Klein, Klein, Moss, & DeMets, 1988), and almost all have already lost 50% of beta cell function (Harris et al., 1992).

Although diabetes is associated with many complications, this review will focus on the four complications assessed in this study: CAD, HF, stroke and RD. A brief overview of other complications (i.e., hypertension, diabetic retinopathy and diabetic neuropathy) is included at the end of the chapter. Although they are beyond the scope of this study, these complications often develop along with CAD, HF, stroke and RD and thus are covered for informational purposes.

2.2.1 Coronary artery disease (CAD)

Cardiovascular disease is the main cause of morbidity and mortality in diabetic patients (Centers for Disease Control and Prevention, 2010; Grundy et al., 1999; Haffner et al., 1998). Results from epidemiologic studies show that hyperglycemia is strongly associated with the development of cardiovascular disease (Coutinho et al., 1999; Khaw et al., 2001; Tuomilehto, 2003). Compared to individuals without diabetes, those with diabetes have a higher prevalence of CAD and coronary ischemia, and are more likely to have myocardial infarctions (MI) and silent myocardial ischemia (Rodbard et al., 2007). The risk of CAD is directly related to the duration

of diabetes (Fox, Sullivan et al., 2004; Miettinen et al., 1998). The US National Cholesterol Education Program (NCEP) report considers T2DM to be a CAD equivalent that increases the occurrence and accelerates the progression of coronary events, strokes, and peripheral arterial disease, placing it in the highest risk category (Antonopoulos, 2002). This classification was based in part upon the observation that patients with T2DM without a history of MI, and patients without diabetes with a history of MI, were at almost the same risk for future MI (20 and 19%, respectively) and coronary mortality (15 and 16%, respectively) (Haffner et al., 1998). Similar findings have been noted in other studies (Libby et al., 2005). Compared to individuals without diabetes, the long and short-term prognoses following a coronary event are worse for diabetes patients, especially women (Hu et al., 2001); the rates for reinfarction, congestive heart failure, and death are increased, and revascularization procedures are less successful (Miettinen et al., 1998). In addition, CAD, when coupled with hypertension, hyperglycemia and elevated lipids, puts diabetics at increased risk not only for myocardial infarction, but also for renal disease (Bakris et al., 2000).

The Framingham Heart Study was the first to report the importance of the association between diabetes and heart disease (Kannel & McGee, 1979b). In the study, the presence of diabetes doubled the age-adjusted risk for cardiovascular disease in men and tripled it in women (Kannel & McGee, 1979b). Diabetes remained a major independent cardiovascular risk factor even when adjusting for increasing age, hypertension, smoking, dyslipidemia, and left ventricular hypertrophy (Kannel & McGee, 1979b).

Most studies of diabetes and CAD compare T2DM diabetics to non-diabetics. In a review of 292 patients with T1DM, heart disease-related mortality increased rapidly after the age of 30, particularly in patients with renal disease (Krolewski et al., 1987). The cumulative CAD

mortality was 35% by age 55, compared to eight and four percent in non-diabetic men and women, respectively, in the Framingham Heart Study (Kannel & McGee, 1979a). Similar relationships were noted for nonfatal MI and angina. When compared to non-diabetics of similar age, the risk for cardiovascular disease in patients with T1DM is even greater than for patients with T2DM (Krolewski et al., 1987).

Even though the incidence of CAD has declined substantially in all adults over the last several decades, diabetic patients are still at greater risk (Fox, Coady et al., 2004). CVD incidence rates were calculated for diabetic and non-diabetic participants aged 45 to 64 years in the Framingham Heart Study, which examined an original cohort between 1950 and 1966 (4,118 participants, 113 with diabetes) and an offspring cohort between 1977 and 1995 (4,063 participants, 317 with diabetes). The CVD incidence rates were compared between the original and offspring cohorts based on main outcome measures of MI, coronary heart disease death, and stroke. Among participants with diabetes, the age- and sex-adjusted CVD incidence rate was 286.4 per 10,000 person-years in the earlier period and 146.9 per 10,000 person-years in the later period, a 49.3% (95% CI [16.7% - 69.4%]) decline (Fox, Coady et al., 2004). Among participants without diabetes, the age- and sex-adjusted incidence rate was 84.6 per 10,000 person-years in the earlier period and 54.3 per 10,000 person-years in the later period, a 35.4% (95% CI [25.3% - 45.4%]) decline (Fox, Coady et al., 2004). Although the age- and sex-adjusted rates for cardiovascular events declined, diabetes was still associated with a two-fold increase in risk (multivariate-adjusted HR 1.96, 95% CI [1.44 - 2.66]) (Fox, Coady et al., 2004).

The role of insulin as a cardiovascular risk factor in T2DM remains controversial. Several prospective studies have investigated the association between insulin therapy and CAD with contradictory results. The U.K. Prospective Diabetes Study (UKPDS) did not find an

association between treatment with insulin and macrovascular outcomes among newly diagnosed diabetic subjects (UKPDS 38, 1998). However, the Feasibility Trial of the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM) initially found a significant increase in cardiovascular events among older veterans with established T2DM who received intensive insulin treatment (Abraira et al., 1997). In a follow-up study, the VA CSDM study group reported that intensive insulin treatment did not affect left ventricular function (Pitale et al., 2000).

2.2.2 Heart failure (HF)

Diabetes mellitus is a well-recognized risk factor for developing heart failure (HF) (Boudina & Abel, 2007). The Framingham Heart Study showed that HF occurs twice as often in diabetic men and five times as often in diabetic women compared with age-matched control subjects (Kannel & McGee, 1979a). In a study of 9,591 patients with T2DM and matched controls, HF was more prevalent at baseline in diabetic subjects (11.8%, n = 1,131) than in control subjects (4.5%, n = 435) (Nichols, Hillier, Erbey, & Brown, 2001). The slopes of the increasing prevalence and incidence of HF across age groups were very similar for subjects with and without diabetes. This suggests that diabetes adds a more or less constant risk of HF, independent of age. Nichols and colleagues (2001) found that the prevalence of HF doubled with each decade of age, confirming an observation reported in the Framingham Heart Study (Kannel & McGee, 1979a).

HF patients with diabetes have poorer survival rates than those who do not have diabetes. In a national sample of Medicare claims of 151,738 beneficiaries, HF was prevalent in 22.3% of the sample in 1994. Among individuals without HF in 1994, the incidence rate for HF over the

five-year study was 12.6 per 100 person-years (95% CI [12.5-12.7 per 100 person-years]) (Bertoni et al., 2004). Incidence was similar by sex and race and increased significantly with age and diabetes-related comorbidities. The adjusted hazard rate for HF increased for individuals with the following: metabolic complications of diabetes (a proxy for poor control and/or severity) (HR 1.23, 95% CI [1.18 - 1.29]), ischemic heart disease (1.74, 95% CI [1.70 - 1.79]), nephropathy (1.55, 95% CI [1.45 - 1.67]), and peripheral vascular disease (1.35, 95% CI [1.31 - 1.39]) (Bertoni et al., 2004). Over 60 months, HF among older adults with diabetes was associated with high mortality, 32.7 per 100 person-years, compared with 3.7 per 100 person-years among those with diabetes who did not develop HF (Bertoni et al., 2004). These data demonstrate a high prevalence, incidence, and mortality for HF in individuals with diabetes.

2.2.3 Stroke

Stroke is a preventable disease that significantly impacts quality of life and is associated with a high cost to society. Preventing stroke in people with diabetes is feasible through identifying and treating risk factors, especially hypertension, cigarette smoking, and dyslipidemia (Air & Kissela, 2007; Kuller, 1995; Rodbard et al., 2007). The incidence and prevalence of stoke among diabetics may be higher now than was suggested in the past due to improved clinical diagnosis through computerized tomography (CT) and magnetic resonance imaging (MRI) (Kuller, 1995). These diagnostic tools identify “silent” strokes and are also used more frequently among older individuals who receive frequent medical care (Kuller, 1995). Given the high prevalence of undetected diabetes in the US population (Centers for Disease Control and

Prevention, 2008, 2011; Rodbard et al., 2007) and the fact that incidence of stroke increases with advanced age, many stroke patients may, in fact, have undetected diabetes when strokes occur.

While significant progress has been made in understanding the link between diabetes and CAD, the scientific literature on diabetes and stroke is less robust. Individuals with T2DM have strokes three times more often than non-diabetics in the general population (Feskens & Kromhout, 1992; Herlitz, Karlson, Lindqvist, & Sjolin, 1998; Kuusisto, Mykkanen, Pyorala, & Laakso, 1994; Rodbard et al., 2007). The results of multiple large randomized controlled trials indicate that blood pressure control reduces morbidity and mortality among patients who have had strokes (Rodbard et al., 2007). Controlling hypertension is critical in preventing stroke, myocardial infarction, and renal failure in diabetics.

The relationship between diabetes and stroke has been substantiated in various studies of racial and ethnic groups (Kissela et al., 2005) women, and older individuals (Air & Kissela, 2007; Sowers, 2003). The greater Cincinnati/Northern Kentucky Stroke Study (GCNKSS), a population-based study of 2,719 African American and white ischemic stroke patients used data extracted from hospital discharge codes and emergency room logs, coroner's cases and sampling in non-hospital settings (Kissela et al., 2005). African Americans in the study cohort were more likely to have diabetes (36%) than whites (30%, $p = 0.005$). In addition, ischemic stroke patients with diabetes were younger (< 55 years old for African Americans, < 65 years old for whites) than the ischemic stroke patients without diabetes. They were also less likely to be current smokers at the time of their strokes and more likely to have been previously diagnosed with hypertension, high cholesterol, and MI. For African Americans, a medical history of diabetes or both diabetes and hypertension was significantly associated with increased risk of stroke (OR 2.7, 95% CI [1.5 - 5.2], OR 3.0, 95% CI [2.1 - 4.3] respectively). Among African Americans,

diabetic stroke patients did not have higher rates of elevated cholesterol, MI, or atrial fibrillation compared to their non-diabetic counterparts, but they did have higher rates of hypertension. For whites, a medical history of diabetes or both diabetes and hypertension was also significantly associated with increased risk of stroke (OR 2.1, 95% CI [1.5 - 3.0], OR 4.5, 95% CI [3.5 - 5.8] respectively). Unlike their African American counterparts, white stroke patients with diabetes did have higher rates of elevated cholesterol and MI compared to those without diabetes, in addition to higher rates of hypertension. Based on the data, Kissela and colleagues (2005) estimate that 25 to 26% of all ischemic strokes can be attributed to the effects of diabetes, either alone or in combination with hypertension; these rates may even underestimate the risk.

Due to the mortality risk associated with stroke, the prevalence data do not adequately represent the magnitude of stroke in the general population (Kuller, 1995). In the Multiple Risk Factor Intervention Trial (MRFIT), 347,978 men aged 35 to 57 years were assessed in 20 centers for baseline vital statistics and risk factors from 1973 to 1975, and then observed over a 12-year period for Cardiovascular Disease (CVD) mortality (Stamler, Vaccaro, Neaton, & Wentworth, 1993). Among 5,163 men who reported taking medication for diabetes, 1,092 died (603 from CVD) during the 12-year observation period. Among the 342,815 men not taking medication for diabetes, 20,867 died, 8,965 from CVD. Absolute risk of CVD death was higher for diabetics than non-diabetics across all ages, races and risk factor levels; overall rates were three times higher when adjusted for age, race, income, serum cholesterol level, systolic blood pressure, and reported number of cigarettes/day ($p < 0.0001$). For men both with and without diabetes, serum cholesterol level, systolic blood pressure, and cigarette smoking were significant predictors of CVD mortality. For diabetic men with higher values for each risk factor and their combinations, absolute risk of CVD death increased more steeply than for non-diabetic men, so that absolute

excess risk for diabetic men was progressively greater than for non-diabetic men with higher risk factor levels (Stamler et al., 1993).

Lower blood pressure is associated with improved cardiovascular outcomes, including reduced risk for nonfatal strokes in diabetics (Air & Kissela, 2007). These results are consistent with other studies that have found the risk of stroke in diabetics to be directly related to other risk factors, especially blood pressure, smoking and dyslipidemia (Air & Kissela, 2007). However, the effect of glycemic control on risk of stroke is less certain than the strong relationship between diabetes and stroke (Air & Kissela, 2007; Kuller, 1995). Published studies provide conflicting evidence. In the Honolulu Heart Program, the risk of stoke was elevated for non-diabetic persons with blood glucose. From 1965 to 1968, the 12-year risk of stroke was examined in 690 diabetic and 6,908 non-diabetic men free of coronary heart disease and without histories of stroke at the beginning of the study. In 12 years of follow-up, 62.3 per 1,000 diabetic men and 32.7 per 1,000 non-diabetic men experienced a stroke. The relative risk of thromboembolic stroke for those with diabetes compared to those without diabetes was 2.0 (95% CI [1.4 - 3.0]) (Abbott, Donahue, MacMahon, Reed, & Yano, 1987). Among those without diabetes, the relative risk of thromboembolic stroke for those at the 80th percentile for serum glucose level (199 mg/dL [11.0mmol/L]) compared with those at the 20th percentile (115 mg/dL [6.4 mmol/L]) was 1.4 (95% CI [1.1 - 1.8]) (Abbott et al., 1987). In the non-diabetic sample, the relative risk of thromboembolic stroke for those with glucose measured in urine compared to those without measurable glucose in urine was 2.7 (95% CI [1.6 - 4.5]) (Abbott et al., 1987). There was no association between diabetes (or measures of glucose intolerance) and hemorrhagic stroke (Abbott et al., 1987). Diabetes, even in a possibly undiagnosed subset of hyperglycemic

individuals, imparts an additional independent risk of stroke unexplained by clinically measured risk factors.

The only clinical trial that has directly evaluated the effect of tight glucose control on stoke is the UKPDS (UKPDS 33, 1998). T2DM patients in the intensive treatment group (average A1C 7.0%) had no significant reduction in stroke incidence ($p = 0.52$) compared with those receiving standard medical therapy (average A1C = 7.9%), indicating that tight glucose control is not sufficient for preventing strokes (UKPDS 33, 1998). It is possible that the study lacked sufficient power to detect the difference or that the treatment intensity level was not sufficient to impact the stroke incidence (Air & Kissela, 2007). Although there is no clear relationship between glycemic control and stroke incidence, diabetics are at increased risk of stroke (Air & Kissela, 2007). The specific mechanisms that underlie the relationship between diabetes and stroke require ongoing investigation to provide new methods for prevention and treatment.

2.2.4 Renal disease (RD)

Diabetes mellitus is the primary cause of renal disease in nonelderly American adults (Perneger et al., 1994), and insulin-dependent diabetics are four times more likely to be diagnosed with end-stage renal disease than non-insulin dependent diabetics (Perneger et al., 1994). Diabetic nephropathy occurs in both T1DM and T2DM, and is the leading cause of renal disease, affecting approximately 40% of diabetic patients (Gross et al., 2005; Levin & Rocco, 2007). It increases the risk of death, mainly from cardiovascular causes, and is defined by increased urinary albumin excretion (UAE) in the absence of other renal diseases (Gross et al., 2005). Hyperglycemia, increased blood pressure levels, and genetic predisposition are the main risk

factors for the development of diabetic nephropathy. Elevated serum lipids, smoking habits, and the amount and origin of dietary protein are also risk factors, though to a lesser degree.

Increased urinary protein excretion is the earliest clinical manifestation of diabetic nephropathy (Levin & Rocco, 2007). The development of microalbuminuria usually begins five to 15 years after the onset of diabetes in patients with T1DM and then increases over time. In a systematic review of nine longitudinal studies examining microalbuminuria in 7,938 patients with TIDM, microalbuminuria was associated with increased long-term mortality. The relative risk for all cause mortality was 1.8% (95% CI [1.5 - 2.1]) compared to patients with normal albuminuria (Newman et al., 2005).

The prevalence of microalbuminuria in patients with T2DM approximately 10 years after diagnosis ranges from 25 to 40% (Adler et al., 2003; Gross et al., 2005; Levin & Rocco, 2007). The prevalence of microalbuminuria varies with ethnicity, with Asians and Hispanics having a higher prevalence than whites (Young et al., 2005). In a cross-sectional study of diabetics with uniform access to care, among those without hypertension, Asians were twice as likely to develop microalbuminuria (OR 2.01, 95% CI [1.14 - 3.53]) and three times more likely to develop macroalbuminuria (OR 3.17; 95% CI [1.09 - 9.26]) than whites (Young et al., 2005). Among those with hypertension, adjusted odds of microalbuminuria were greater for Hispanics (OR 3.82, 95% CI [1.16 - 12.57]) than whites, whereas adjusted odds of macroalbuminuria were threefold greater for blacks (OR 3.32, 95% CI [1.26 - 8.76]) than for whites (Young et al., 2005).

Some patients with T2DM have microalbuminuria at the time of diagnosis (Adler et al., 2003). A possible explanation for the presence of microalbuminuria at the time of T2DM diagnosis is previously undiagnosed diabetes or some other pathology. The UKPDS, which studied approximately 5,100 patients with newly-diagnosed T2DM, reported that 6.5% of the

cohort had microalbuminuria and 0.7% had macroalbuminuria at the time of diagnosis. From diagnosis of T2DM, the progression to microalbuminuria occurs at 2.0% per year, and from microalbuminuria to macroalbuminuria at 2.8% per year (Adler et al., 2003).

2.2.5 Other complications

2.2.5.1 Hypertension

Hypertension occurs approximately twice as frequently in diabetics than in people without the disease (Sowers, Epstein, & Frohlich, 2001). Approximately 25% of individuals with T1DM and more than 50% of individuals with T2DM have hypertension (Rodbard et al., 2007). However, recent data suggest that hypertensive persons are more predisposed to the development of diabetes than normotensive persons (Sowers et al., 2001). In a large, prospective cohort study that included 12,550 adults, the development of T2DM was almost 2.5 times as likely in persons with hypertension than in their normotensive counterparts (Gress, Nieto, Shahar, Wofford, & Brancati, 2000). Overall, research suggests that diabetes and hypertension, two common chronic diseases, frequently coexist (Sowers et al., 2001). Furthermore, the pathology of each chronic disease entity, although independent in its own natural history, serves to exacerbate the other (Sowers & Epstein, 1995; Sowers et al., 2001).

There is a close relationship between hypertension and increasing albuminuria in diabetics. A study of 981 patients who had T1DM for five or more years reported hypertension in patients with normoalbuminuria (19%), microalbuminuria (30%) and macroalbuminuria (65%) (Parving et al., 1988). The findings are different in patients with T2DM. In a cross-sectional study of 3,500 newly diagnosed T2DM patients recruited for the UKPDS, 39% (35% of the males and 46% of the females) were hypertensive (i.e., had mean blood pressure $\geq$ 160

mm Hg systolic and/or ≥ 90 mm Hg diastolic at two and nine months after diagnosis of diabetes, or received antihypertensive therapy) (Turner et al., 1993). The hypertensive patients also had a greater mean body mass index (30.1 versus 28.0 kg/m2, $p < 0.0001$) than the normotensive patients (Turner et al., 1993), showing a relationship with obesity.

Hypertension also represents a serious risk for diabetics because it amplifies the effects of hyperglycemia in producing microvascular complications (Rodbard et al., 2007). For macrovascular complications such as stroke and ischemic heart disease, hypertension is a more clinically significant risk factor than hyperglycemia itself (Adler et al., 2000).

2.2.5.2 Diabetic retinopathy

Diabetic retinopathy is an increasingly important cause of visual loss. The National Health and Nutrition Examination Survey (NHANES) reported that 11% of patients aged 20 years and older with diabetes have visual impairment (Zhang et al., 2006). The prevalence of diabetic retinopathy increases with the duration of diabetes (Klein, Klein, Moss, Davis, & DeMets, 1984). Additional risk factors include glycemic control, the type of diabetes (type 1 more than 2), and the presence of associated conditions such as hypertension, smoking, nephropathy, dyslipidemia, and pregnancy. Impairments are usually correctable with prescription glasses or contact lenses; nonetheless, data support the need for vision screening in addition to dilated eye examinations for retinopathy among diabetics.

2.2.5.3 Diabetic neuropathy

Foot problems are an important cause of morbidity in patients with diabetes mellitus. Among persons diagnosed as having diabetes mellitus, the prevalence of foot ulcers is four to 10% (whereas the annual population-based incidence is 1.0 to 4.1%), and the lifetime incidence may

be as high as 25% (Singh, Armstrong, & Lipsky, 2005). Several risk factors are predictive of ulcers and amputation. The most important are previous foot ulceration, neuropathy (loss of protective sensation), foot deformity, and vascular disease (Singh et al., 2005).

Neuropathy is present in over 80% of patients with foot ulcers (Singh et al., 2005). Neuropathy promotes ulcer formation by decreasing pain sensation and perception of pressure, causing muscle imbalance that can lead to anatomic deformities and impair the microcirculation and the integrity of the skin. Once ulcers form, healing may be delayed or difficult to achieve, particularly if infection penetrates to deep tissues and bone and/or there is diminished local blood flow. The significance of these risk factors was confirmed by the results of a community-based study of 1,300 patients with T2DM in the Fremantle Diabetes Study (Davis, Norman, Bruce, & Davis, 2006). The incidence of lower extremity amputation (LEA) was 3.8 per 1,000 patient-years. Predictors of amputation were foot ulceration (HR 5.6, 95% CI [1.2 - 25), ankle brachial index < 0.9, elevated A1C, and neuropathy. First-ever LEAs in T2DM patients were associated with poor glycemic control, foot ulceration and evidence of microvascular and macrovascular disease. Patients with LEA were also at increased risk of cardiac death (Davis et al., 2006).

2.3 INTERVENTIONS

Effective management of diabetes requires persistent monitoring and therapy adjustment (Turner et al., 1995). Findings from large randomized controlled trials provide evidence that intensive treatment of diabetes mellitus and conditions known to be risk factors can significantly decrease the development and/or progression of chronic complications (DCCT, 1993, 1996; EDIC, 1999;

ETDRS, 1991; Goldberg et al., 1998; Knowler et al., 2002; Litzelman et al., 1993; Mann, 2000; Ohkubo et al., 1995; Rodbard et al., 2007; Stratton et al., 2000; UKPDS 33, 1998; UKPDS 38, 1998; UKPDS 40, 1998). Specific benefits are derived by monitoring and controlling glycemia, blood pressure and lipids, screening for microalbuminuria and retinopathy, and conducting routine foot examinations (Saaddine et al., 2006). To achieve greater risk reduction, the American Diabetes Association, the American Association of Clinical Endocrinologists, and the Diabetes Quality Improvement Alliance recommend more aggressive interventions at earlier stages in the disease process (American Diabetes Association, 2010; Feld, Hellman, & Dickey, 2002; Fleming et al., 2001). Such treatments include: (a) lifestyle modifications, such as dietary changes, weight reduction, exercise, and smoking cessation; (b) pharmacologic treatments, such as statins that effectively prevent both primary and secondary cardiovascular events and decrease mortality; (c) intensive control of glycemia and hypertension; and (d) aspirin as a secondary prevention for vascular events.

2.3.1 Glycemic control

Although diabetes is treated and managed using a multifaceted approach to address both primary causes and complications of the disease, glycemic control remains a primary focus in any treatment plan. Much research has focused on glycemic control and its role in mitigating complications associated with diabetes. New pharmacologic therapies and treatment technologies safely and effectively lower blood glucose to near-normal levels (American Diabetes Association, 2010; Rodbard et al., 2007). In addition to new rapid-acting and long-lasting insulin analogs, new medications have been introduced to address recently identified pancreatic hormone and incretin hormone deficiencies (Kendall et al., 2005; Rodbard et al.,

2007; Samsom et al., 2000). These new medications and similar therapies in development effectively lower A1C levels, thereby reducing glycemic variability and weight (Kendall et al., 2005; Samsom et al., 2000). Technical advances such as continuous blood glucose monitoring mechanisms and insulin pumps provide clinicians and patients with useful tools to monitor and adjust treatment regimens (Rodbard et al., 2007).

2.3.1.1 Glycemic control and microvascular complications

Hyperglycemia is an important risk factor in the development of microvascular disease, and several major studies have found that intensive glycemic monitoring and control significantly reduces microvascular complications (DCCT, 1993, 1996; Duckworth et al., 2009; Klein, 1995; Margetts, 1995; Nathan et al., 2005; Newman et al., 2005; Phillips & Molitch, 1995; UKPDS 33, 1998). The UKPDS study assessed different treatment regimens on glycemic control and diabetes complications in 4,000 newly diagnosed patients with T2DM (Holman, Cull, Fox, & Turner, 1995). Over a period of 10 years, average A1C values were lower in the intensive therapy group, and the risk for any diabetes related endpoint was 12% lower ($p = 0.029$), with most of the risk reduction being due to a 25% risk reduction in microvascular disease ($p = 0.001$) (Margetts, 1995; UKPDS 33, 1998). In addition, there was no evidence of a threshold effect for A1C; a 1% decrease in A1C was associated with a 35% reduction in microvascular disease outcomes (Margetts, 1995; UKPDS 33, 1998). The benefits of intensive therapy appeared to be independent of the type of treatment administered. Furthermore, the results of the UKPDS post-trial monitoring phase show that for newly diagnosed T1DM patients, sustained glycemic control provides a lasting benefit of reducing microvascular disease (UKPDS 33, 1998). Notably, although A1C values decreased along with microvascular disease risk, there was no statistically significant reduction in macrovascular disease (UKPDS 33, 1998).

As in the UKPDS, compliance with targets established for glycemic control was found to prevent the onset and progression of microvascular complications from diabetes such as nephropathy, retinopathy, and neuropathy (DCCT, 1993, 1996; DCCT/EDIC, 2000; Phillips & Molitch, 1995). A 1% reduction in A1C was found to reduce microvascular complications by 30% (DCCT, 1993).

The Pittsburgh Epidemiology of Diabetes Complications (EDC) study was an observational study of patients with T1DM (Nathan et al., 2009). The study population consisted of the DCCT T1DM cohort (N = 1,441) and a subset of the EDC cohort (n = 161) selected to match DCCT entry criteria. In the DCCT, intensive therapy aimed for a near-normal glycemic level with three or more daily doses of insulin. Conventional therapy, with one to two daily doses of insulin, was not designed to achieve specific glycemic targets. Main outcome measures included incidences of diabetic retinopathy, nephropathy (albumin excretion rate > 300 mg/24 h or renal replacement), and cardiovascular disease (Nathan et al., 2009). After 30 years of observation, the cumulative incidences of diabetic retinopathy, nephropathy, and cardiovascular disease were 50%, 25%, and 14%, respectively, in the DCCT conventional treatment group, and 47%, 17%, and 14%, respectively, in the EDC cohort (Nathan et al., 2009). The DCCT intensive therapy group had substantially lower cumulative incidences (21%, 9%, and 9%) and less than 1% became blind, required kidney replacement, or had an amputation related to diabetes during that time (Nathan et al., 2009). The EDC study provides further evidence that the frequency of serious complications in patients with T1DM who are treated intensively are lower than previously reported.

The Veteran's Affairs Diabetes Trial of Glycemic Control and Complications in Diabetes Mellitus Type 2 (VADT) was a longer term prospective study of 1,791 veterans with T2DM

(Duckworth et al., 2009). Diabetics were randomly assigned to either intensive or conventional therapy. The treatment goal for the intensive therapy group was to achieve normal A1C measurements. After an approximate five-year observation period, the intensive therapy group achieved an average A1C measurement of 6.9% (HR = 1.07, 95% CI [0.74 - 1.05]) compared to the conventional therapy group, with an average A1C measurement of 8.4%; however, there was no difference in the first occurrence of any cardiovascular event (such as stroke, death from other cardiovascular causes, heart failure, surgery for vascular disease, or amputation) between the two treatment groups (Duckworth et al., 2009).

The results of both UKPDS studies and the DCCT are consistent: intensive therapy decreases outcomes of microvascular disease (DCCT, 1993, 1996; DCCT/EDIC, 2000; Duckworth et al., 2009; Margetts, 1995; Nathan et al., 2005; Nathan et al., 2009; Phillips & Molitch, 1995; UKPDS 33, 1998). Such intensive control did not provide the same benefit in the VADT, but this may be due to the fact that participants had been diagnosed with diabetes for a longer period of time (mean of 11.5 years compared to newly diagnosed in UKPDS) and time is required to yield benefits, requiring longer follow up, and intensive treatment of hypertension and hyperlipidemia (Duckworth et al., 2009).

Complying with targets established for glycemic control reduces the risk of early onset and progression of microvascular complications from diabetes such as nephropathy, retinopathy, and neuropathy (DCCT, 1993; DCCT/EDIC, 2000; Mohamed, Gillies, & Wong, 2007; Newman et al., 2005; Phillips & Molitch, 1995; UKPDS 33, 1998).

2.3.1.2 Glycemic control and macrovascular complications

Several studies suggest a correlation between chronic hyperglycemia and higher rates of macrovascular complications (i.e., cardiovascular disease) (Gerstein et al., 2007; Kelly et al.,

2009; Selvin et al., 2004). In Selvin's (2004) meta-analysis of thirteen prospective studies, for every 1% increase in A1C, the relative risk for any cardiovascular event is 1.18 (95% CI [1.10 - 1.26]). Although these studies suggest that improvements in A1C may reduce cardiovascular outcomes, most randomized clinical trials have not demonstrated a beneficial effect of intensive therapy (Duckworth et al., 2009; Margetts, 1995; UKPDS 33, 1998). The VADT trial was designed to study the effects of intensive versus conventional therapy on cardiovascular outcomes in subjects with longstanding diabetes (average duration eight to 12 years); results show no benefit in macrovascular outcomes from intensive control (Duckworth et al., 2009). In fact, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial actually showed a significant *increase* in total and CAD-related mortality with intensive therapy (Buse et al., 2009; Gerstein et al., 2007).

However, meta analyses have demonstrated a reduction in the risk of heart disease (RR 0.89, 95% CI [0.81 - 0.96]) and non-fatal MI (RR 0.84, 95% CI [0.75 - 0.94]) with intensive decreases in blood glucose versus standard treatment (Kelly et al., 2009; Ray et al., 2009). Nathan and colleagues (2005) report that early and aggressive glycemic control in patients with T1DM lowers the risk for cardiovascular disease by 50%. There is no glycemic threshold for the reduction of complications in T1DM; essentially, the better the control, the lower the risk (Stratton et al., 2000). Klein (1995) also found that glycemic control is associated with lower risk of CAD and other macrovascular diseases.

The contradictory findings in studies on T2DM may be due to differences in study designs, pharmacologic therapy choices and baseline glycemic control. In newly diagnosed patients with T2DM, glycemic control as measured by A1C is achievable; however, its role in preventing or reducing macrovascular complications is uncertain. Although advances have been

made in the ability to reduce cardiovascular morbidity and mortality in patients with diabetes mellitus, the average risk reduction is only 25 to 35%, and patients are still at significant residual risk for cardiovascular disease (Rodbard et al., 2007).

2.3.2 Microalbuminuria screening

Screening for microalbuminuria is important, as it predicts later development of diabetic nephropathy. Even so, individuals with macroalbuminuria are more likely to die in any year than to develop renal failure (Adler et al., 2003). This is partially due to the fact that microalbuminuria is also associated with arterial hypertension, diabetic retinopathy, blindness, and peripheral neuropathy. Microalbuminuria can be both a symptom and a predictor of complications. For instance, microalbuminuria is a predictor of diabetic nephropathy, and patients with increasing nephropathy experience increasing risk of cardiovascular death ($p < 0.0001$), with an annual rate of 0.7% for subjects in the stage of no nephropathy, 2.0% for those with microalbuminuria, 3.5% for those with macroalbuminuria, and 12.1% with elevated plasma creatinine (Adler et al., 2003). Thus, urinary excretion of albumin should be monitored routinely in patients with insulin dependent diabetes (Parving et al., 1988).

Screening for microalbuminuria should be performed yearly, starting five years after diagnosis for patients with T1DM, or earlier in the presence of puberty or poor metabolic control. In patients with T2DM, screening should be performed at diagnosis and yearly thereafter. Patients with micro- and macroalbuminuria should undergo an evaluation regarding the presence of other comorbidities, especially retinopathy and other evidence of macrovascular disease (Levin & Rocco, 2007).

Treating microalbuminuria is complex and multi-faceted. Achieving high metabolic control (A1C < 7%), treating hypertension (<130/80 mm Hg or <125/75 mm Hg if proteinuria > 1.0 g/24 h and increased serum creatinine), using drugs with blockade effects on the renin-angiotensin-aldosterone system, and treating dyslipidemia (LDL cholesterol < 100 mg/dl) are effective strategies for preventing the development of microalbuminuria, delaying the progression to more advanced stages of nephropathy, and reducing cardiovascular mortality in patients with T1DM and T2DM (Gross et al., 2005; Levin & Rocco, 2007). Research results are variable regarding the efficacy of ACE inhibitors or ARBs for the primary prevention of microalbuminuria in clinical trials with T2DM patients (Parfrey, 2009; Strippoli, Craig, Schena, & Craig, 2005).

2.3.3 Lipid control

Aggressive lipid management is important in reducing morbidity and mortality in diabetics. While treatment for individuals with diabetes has traditionally focused on glycemic control to reduce vascular complications, there is growing evidence highlighting the importance of controlling cholesterol levels (Saydah et al., 2004). Good lipid control can reduce the risk of coronary heart disease by 25 to 55% and risk of death by 43% (Goldberg et al., 1998).

Studies have observed differences in the lipid profiles of T1DM and T2DM patients and between diabetics and non-diabetics that may contribute to the increase in CAD. The lipid pattern in patients with T1DM is largely related to glycemic control. The DCCT found that patients with T1DM (mean A1C of 8.8%) had serum lipid values similar to those of non-diabetics in the Lipid Research Clinics (LRC) prevalence study, except for young women, who had somewhat higher serum total cholesterol and lower high-density lipoprotein (HDL)

cholesterol concentrations (DCCT, 1992). Lipid and lipoprotein levels in the generally healthy IDDM volunteers for the DCCT were similar to those in the non-diabetic population (DCCT, 1992). Insulin resistance, insulin deficiency and obesity are associated with elevated triglycerides and low serum HDL cholesterol concentrations and high LDL cholesterol in T2DM (O'Brien, Nguyen, & Zimmerman, 1998).

The association of elevated LDL cholesterol with cardiovascular risk in many epidemiologic studies has been reinforced by randomized clinical trials showing that statin therapy improves outcomes in diabetics, including those without clinical evidence of CAD and those with values below 116 mg/dL (3 mmol/L) (Rodbard et al., 2007). The primary goal is to reduce the LDL-C level to less than 100mg/dL; in high risk individuals, the LDL goal is less than 70 mg/dL (Rodbard et al., 2007). Cardiovascular markers such as C-reactive protein and lipoprotein associated phospholipase A2 may assist in identifying high risk patients and initiating preventive measures (Rodbard et al., 2007).

2.3.4 Other interventions

2.3.4.1 Hypertension control

The results of multiple large randomized controlled trials indicate that blood pressure control also reduces morbidity and mortality among diabetics (Adler et al., 2000; Saydah et al., 2004); in fact, just a 10 mm Hg reduction in blood pressure reduces macrovascular and microvascular complications and risk of death by 35% (UKPDS 33, 1998; UKPDS 38, 1998). Up to 75% of vascular disease in diabetes may be attributable to hypertension, leading to recommendations for more aggressive treatment (i.e., reducing blood pressure to < 130/85 mm Hg).

All hypertensive diabetics benefit from lowering blood pressure (Gross et al., 2005; Newman et al., 2005). The prevalence and time of development of hypertension varies for T1DM and T2DM patients. ACE inhibitors and ARBs are often prescribed for hypertension, and have been found to reduce disease progression and mortality.

It is important to note that some studies on non-diabetic hypertensive patients have noted a higher risk for the development of diabetes when certain medications are taken. In one study, hypertensive patients who took beta blockers had a 28% higher risk of developing diabetes than did those who took no medication , whereas those who took thiazide diuretics, ACE inhibitors, or calcium antagonists were found not to be at greater risk for subsequent diabetes than were patients who were not receiving any antihypertensive medications (Gress et al., 2000). Other randomized prospective trials have not shown an increase in the development of diabetes with beta blocker or low-dose diuretic treatment of hypertension (Sowers et al., 2001). In contrast, the HOPE Study reported that ACE inhibitor therapy *reduced* the propensity of hypertensive patients to develop T2DM by 11% and 34% in six- and four-year trials, respectively, suggesting that antihypertensive treatment may significantly decrease the risk of diabetes development in this population (Sowers et al., 2001; Yusuf et al., 2000).

2.3.4.2 Retinopathy interventions

Proper screening (e.g., dilated fundus examination), glycemic and hypertension control, and early interventions incorporating both surgical and pharmacologic therapies can help diabetics avoid severe vision loss associated with diabetic retinopathy (Mohamed et al., 2007). Specific treatments include: pan-retinal laser photocoagulation, focal laser photocoagulation and early vitrectomy. When conventional treatments fail, intravitreal steroid injections may be considered for eyes with persistent loss of vision (Mohamed et al., 2007).

2.3.4.3 Neuropathy interventions

Substantial evidence supports screening all patients with diabetes to identify those at risk for foot ulceration. Prevention of diabetic foot ulcers begins with screening for loss of protective sensation. Specialist clinics may quantify neuropathy with biothesiometry, measure plantar foot pressure, and assess lower extremity vascular status with Doppler ultrasound and ankle-brachial blood pressure indices. These measurements, in conjunction with patient medical histories and physical examinations, enable clinicians to stratify patients based on risk to determine the types of interventions required (Singh et al., 2005).

Educating patients about proper foot care and conducting periodic foot examinations are effective interventions to prevent ulceration. Other possibly effective clinical interventions include glycemic control optimization, smoking cessation, intensive podiatric care, debridement of calluses, and certain types of prophylactic foot surgery (Singh et al., 2005). The value of various types of prescription footwear for ulcer prevention is not clear (Singh et al., 2005).

2.4 CLINICAL CARE PROCESSES AND OUTCOMES

Optimal diabetes care depends on healthcare providers adhering to evidence-based practice guidelines in the delivery of care, and patients adhering to self-management recommendations in order to maximize intermediate outcomes and reduce complications (Ward et al., 2004). Process measures assess the degree to which providers follow the evidence-based practice guidelines (e.g., the percentage of patients with two A1C tests in a year, at least one lipid test in a year, at least one screen for microalbuminuria in a year, etc.). Outcome measures assess the

extent of glycemic, lipid, and blood pressure control in patients with diabetes (e.g., the percentage of patients with a measured A1C < 7% and a measured low-risk lipid cholesterol (LDL) value ≤ 100 mg/dl). Process and outcome measures are distinct and complementary aspects assessing quality of diabetes care, and the relationship between processes of care and patient outcomes is a central issue in health services research.

2.4.1 Process measures

For most of the 20th century, diabetes care has been suboptimal and varied in the United States (Beckles et al., 1998; Engelgau et al., 1998; Fleming et al., 2001; Kenny et al., 1993; Saaddine et al., 2006). Founded in 1997, the National Diabetes Quality Improvement Project developed a comprehensive set of measures to assess quality of care for diabetes patients that are now considered standard (Fleming et al., 2001). Annual screenings for lipids and microalbuminuria and at least two measurements of A1C are recommended as well as annual flu vaccinations, dilated eye exams and biannual foot examinations (American Diabetes Association, 2005). These measures were incorporated into the HEDIS, the American Diabetes Association Provider Recognition Program, the American Medical Association Diabetes Measures Group, the Veterans Administration's performance monitoring program, and other standards. With the establishment of national performance measures, researchers have been provided with a unique opportunity to assess the provision and quality of successful treatment of diabetes and many other chronic diseases.

In terms of adhering to recommended clinical care processes, quality has improved over the past 10 years (Saaddine et al., 2006). Although the level of care in the US continues to fall short of what is recommended, annual lipid testing, dilated eye and foot examinations, self-

monitoring of blood glucose levels, adherence to aspirin therapy and pneumococcal and influenza vaccination rates have improved significantly (Saaddine et al., 2006). Cross-sectional observational data on the quality of medical care for six medical conditions including diabetes yielded similar results (Jencks et al., 2003). Using three performance indicators from the National Committee for Quality Assurance (NCQA) and HEDIS guidelines, the study found that the percentage of Medicare fee for service beneficiaries receiving appropriate diabetes preventive care services in the median state improved from the first observational period (1997 to 1999) to the second (2000 to 2001), from 71 to 78% for A1C testing, 69 to 70% for eye exams and 57 to 74% for cholesterol testing (Jencks et al., 2003).

2.4.2 Outcome measures

Despite well-documented benefits of process improvements in diabetes treatment, the changes in intermediate patient outcomes (e.g., sustained control of A1C) are surprisingly minimal (Selby et al., 2007). In fact, diabetes control in American patients deteriorated over the past decade (Koro et al., 2004; Rodbard et al., 2007; Saaddine et al., 2006). The percentage of T2DM patients with A1C levels of less than 7% decreased by approximately 20% from 1988 to 2000 (Koro et al., 2004). Selby and colleagues (2007) found that among people with diabetes, one in five (2.2 million) has poor glycemic control (A1C $\geq$ 9%), two in five (3.6 million) have poor LDL cholesterol level control ($\geq$ 3.4 mmol/L or 130 mg/dL), one in three (3.5 million) has poor blood pressure control ($\geq$ 140/90 mm Hg), and one in three has not received annual eye (3.2 million) or foot (3.1 million) examinations. In addition, most patients with diabetes in the United States have values for intermediate clinical outcomes that exceed target levels: 58% have A1C $\geq$ 7%, 66% have LDL levels $\geq$ 100 mg/dl, and 52% have systolic blood pressure $\geq$ 130 mm Hg

(Saaddine et al., 2006). In academic-based health care settings, only 7% of patients with T1DM or T2DM achieve the three recommended goals for glycemia, lipids, and blood pressure (Grant et al., 2005). These findings are consistent with another recent report (Jencks et al., 2003) highlighting the need for continued efforts to improve intermediate outcomes and noting several implications for future quality improvement strategies.

Another study also recognizes a gap between recommended diabetes care and patient outcomes (Saaddine et al., 2002). Saaddine and colleagues (2002) analyzed data from the third U.S. National Health and Nutrition Examination Survey (NHANES III) (1988-1994) and the Behavioral Risk Factors Surveillance System (BRFSS) (1995). The analysis revealed that 18.0% of participants (95% CI 15.7% to 22.3%) had poor glycemic control (A1C > 9.5%), and 65.7% (CI 62.0% to 69.4%) had blood pressure less than 140/90 mm Hg. Although cholesterol was monitored biannually in 85.3% (CI 83.1% to 88.6) of participants, only 42.0% (CI 34.9% to 49.1%) had LDL cholesterol levels less than the recommended < 130 mg/dL) (Saaddine et al., 2002). In addition, persons taking insulin were more likely to have poor glycemic control (24.2%, CI 18.3% to 30.1%) than other patients (15.5%, CI 11.6% to 19.4%) (Saaddine et al., 2002).

Saaddine and colleagues (2006) later updated their analysis by examining the same data (NHANES and BRFF) from 1999 through 2002. The proportion of diabetics with poor glycemic control (A1C > 9%) showed a non-statistically significant decrease of 3.9% (95% CI 2.5% to 10.4%). Annual lipid testing increased by 8.3% (CI 4.0% to 12.7%), and the proportion of patients with fair or good lipid control (LDL cholesterol level > 130 mg/dL) showed a statistically significant increase of 21.9% (CI 12.4% to 31.3%), while mean LDL cholesterol levels decreased by 0.5 mmol/L (18.8 mg/dL). Although mean A1C did not change, the

proportion of persons with A1C measurements of six to 8% increased from 34.2% to 47.0%. The blood pressure distribution did not change. Recent reports using national data also show improvement in cardiovascular disease risk factors among people with diabetes between NHANES III and NHANES 1999–2000 (Imperatore et al., 2004; Saydah et al., 2004).

Thus, improvements in lipid control and some improvement in glycemic control have occurred, but blood pressure control has not improved (Saaddine et al., 2006). These findings are consistent with the results reported in specific populations and health care systems, such as the Veterans Health Administration (Sawin et al., 2004), Indian Health Service (Roubideaux et al., 2004), managed care organizations (McClain et al., 2003), and Medicare (Jencks et al., 2003).

2.4.3 Summary

Although it has not been firmly established that early detection of T2DM and intervention actually improves long-term outcomes, a computer simulation model of subjects over age 25 suggests that the cost increases associated with screening and early treatment may be worth it (Engelgau et al., 1998). However, it should be noted that the benefits of early detection in the model were derived more from postponement of complications from diabetes than from additional life-years. In other analyses, targeting individuals with hypertension was more effective than universal screening, and screening for impaired glucose tolerance and undiagnosed T2DM followed by intervention was more cost effective than no screening at all (Gillies et al., 2008).

Given the large number of Americans with undiagnosed diabetes mellitus, early detection and treatment is imperative to addressing the diabetes epidemic (Centers for Disease Control

and Prevention, 2008; Rodbard et al., 2007). The most commonly used screening measurements for diagnosing T2DM include fasting plasma glucose (FPG), two-hour plasma glucose during an oral glucose tolerance test, glycosylated hemoglobin (A1C), and urine glucose. In June 2009, the International Expert Committee issued a consensus report recommending that A1C tests be used to diagnose diabetes (Nathan, 2009). In making the recommendation, the report noted several advantages of the A1C screen over glucose testing, including increased patient convenience and the correlation of glycosylated hemoglobin levels with retinopathy (Nathan, 2009). At the same time, it should be noted that urine glucose is an insensitive method of screening for diabetes; the high rate of false negative results suggests that it is not adequate as a screening test (Andersson, Lundblad, & Svärdsudd, 1993). Additionally, not all patients with glucose in their urine have diabetes since it also occurs when defects in renal tubular function exist (Calado et al., 2006).

Consistent with ADA guidelines (American Diabetes Association, 2010), measurement of fasting blood glucose is recommended for individuals aged 45 years or older and those who are considered high risk. High risk individuals are those with body mass indexes (BMI) of 25 kg/m^2 or more, and one or more additional risk factors for diabetes, including: family history of diabetes, personal history of delivering a baby weighing more than nine pounds or gestational diabetes, hypertension, dyslipidemia, habitual physical inactivity, or ethnicity (i.e., African American, Hispanic, Native American, Asian American and Pacific Islander).

Microvascular complications of diabetes mellitus affecting the kidneys (Fong et al., 2004; Gross et al., 2005), retinas (Fong et al., 2004; Frank, 2004), and nerves (Vinik et al., 2003) may be apparent to a medical examiner before a patient experiences any symptoms. While some preventive screening and treatment strategies are applicable for all microvascular diseases, others are organ-specific. A program of periodic preventive monitoring can detect asymptomatic

disease that may be responsive to specific therapy aimed at interrupting disease progression or reversing the abnormality (Gæde, Vedel, Parving, & Pedersen, 1999; Klein et al., 1991; Lewis et al., 2001). Indicators of microvascular complications are: (a) microalbuminuria ≥ 30 mg albumin/g; (b) creatinine and blood pressure ≥ 130/80 mm Hg (c) use of angiotensin-converting enzyme (ACE) inhibitors, which delay the progression of nephropathy in patients with T1DM who have hypertension and any degree of albuminuria (Bakris et al., 2000); and (d) the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARBs), which may slow the progression of microalbuminuria in patients with T2DM, hypertension and renal insufficiency (serum creatinine >1.5 mg/dL) (Lewis et al., 2001). Measuring both processes and outcomes contributes to a better understanding of how to improve the quality of diabetes care; yet a review of 41 studies on diabetes management in primary care, outpatient and community settings, shows that only 15 reported both patient outcomes and process measures (Renders et al., 2001). Measuring care processes and patient outcomes in isolation yields incomplete results and ignores important implications for diabetes care; the two should not be separated.

Although the quality of diabetes care appears to be increasing, opportunities remain for further improvement. It is important to note that the percentages of self-reported performance measurements obtained from member surveys are almost always higher (sometimes substantially higher) than the percentages based on medical record abstracts or administrative data (Fowles, Rosheim, Fowler, Craft, & Arrichiello, 1999). Self-report performance measurements likely contributed to statistical improvements in the quality of diabetes care in the United States over the past 10 years. It is important to continue to study adherence to recommended processes and patient outcomes *together* to truly assess improvement and to make better recommendations for diabetes care in the future.

2.5 ACCESS TO CARE

The availability of health insurance is a strong factor associated with better process and outcome measures (Saaddine et al., 2002). In a major study, after controlling for age, sex, ethnicity, education, insulin use and duration of diabetes, insured persons were less likely to have A1C levels greater than or equal to 9.5% (Saaddine et al., 2002). In the United States, where per capita health care costs are the highest in the world and continue to escalate, health insurance has become almost essential to accessing appropriate diabetes care. Reasonable access to health care depends on many factors, including the availability of health services in a community and personal care-seeking behavior. However, these and other factors are often trumped by whether a person can afford the costs of needed care.

Health insurance enables access to care by protecting individuals and families against the high and often unexpected costs of medical care and connecting them to networks and systems of health care providers (Hoffman & Paradise, 2008). Although private and public health insurance plans are available in the United States, the American health insurance system is largely comprised of employer-based coverage for working adults and Medicare for the elderly and disabled.

Most working age adults obtain health coverage for themselves and their dependents as a benefit of employment. However, this benefit has been eroding gradually as health premiums, along with higher health care costs, grow at rates outpacing general inflation and wages (Hoffman & Paradise, 2008; Institute of Medicine Committee on Health Behavior, 2001). In 2005, just 61% of the nonelderly had insurance through an employer, down from 66% in 2000 (Hoffman & Paradise, 2008). Not surprisingly, low-wage employees are far less likely than higher-wage employees to have access to job-based coverage (Hoffman & Paradise, 2008). In

2003, more than half of employees in poor families and more than a third of those in near-poor families had no job-based coverage available for their families (Clemans-Cope, Garrett, & Hoffman, 2006). Even when it is available, health insurance is often unaffordable for low-income people (Clemans-Cope et al., 2006; Kaiser Commission on Medicaid and the Uninsured, 2007).

Health services research shows a strong association between health insurance coverage and access to primary and preventive care, the treatment of acute and traumatic conditions, and the medical management of chronic illnesses such as diabetes (Hoffman & Paradise, 2008). The same research connects being uninsured with adverse health outcomes, including declines in health and functioning, the existence of preventable health problems, severe disease at the time of diagnosis, and premature mortality (Hoffman & Paradise, 2008; Institute of Medicine, 2002). Although health insurance alone would neither eliminate disparities in access to health care nor equalize health across subgroups of Americans, having health insurance is clearly connected to a longer life of better quality (Institute of Medicine, 2002).

Disparate access to quality health care is a common explanation for socioeconomic and ethnic disparities in diabetic complication rates within the US population (Selby et al., 2007; Smedley et al., 2002). Population-based studies suggest that racial and ethnic minorities and people of lower socioeconomic status (SES) experience worse long term diabetes outcomes than whites and people of higher SES (Brown et al., 2005). Other studies have shown less adherence to processes of diabetes care (dilated retinopathy, etc) and worse intermediate outcomes among racial and ethnic minorities and individuals with lower incomes or education levels (Karter et al., 2002; Lanting, Joung, Mackenbach, Lamberts, & Bootsma, 2005). Since racial and ethnic minorities and poorer people with diabetes are less adequately insured than whites or people

higher on the SES ladder (Brown et al., 2005), differential access to care may contribute to these observations. Research from managed care settings (Karter et al., 2002; Martin et al., 1995) and the Veterans Health Administration (Heisler et al., 2003; Young et al., 2003) suggest that racial and ethnic disparities in diabetes processes and outcomes may be reduced in settings offering more uniform access to care. In the TRIAD research, 7,456 adults who were enrolled in health plans participated in a six center cohort study on diabetes treatment and outcomes in a managed care setting; minority race and ethnicity were consistently associated with worse processes or outcomes (Brown et al., 2005).

It is unknown whether recent improvements in health care options for diabetes have benefited all groups equally, or whether, as noted in earlier studies (Karter et al., 2002), socioeconomic differences that lead to substandard health care for minorities remain. However, it is clear that access to care and associated variables such as SES and ethnicity are conflated with quality of diabetes care in many research studies using participant samples from the general population. Thus, studies of insured populations provide an important complement to population based studies by controlling for access to care.

2.6 RESEARCH JUSTIFICATION

Changing demographics in the US population will only fuel the diabetes epidemic, and many more people will be stricken with the disease in the years to come (Centers for Disease Control and Prevention, 2008). Ensuring access to and delivery of high-quality care for all people with diabetes should be a national priority, as it has serious financial and social implications.

Understanding how to better implement existing diabetes care interventions with minimal resources will be critical to ensuring the highest possible quality of life for millions of Americans afflicted with the disease.

Understanding diabetes risk factors is challenging, yet essential for preventing diabetes complications. Most of the diabetes care literature focuses on adherence to patient care processes or patient outcomes – not both (Renders et al., 2001). Despite advances in diabetes research and consensus recommendations for diabetes care, adherence to patient care processes and intermediate health outcomes are still falling short of targeted levels (Saaddine et al., 2006; Saaddine et al., 2002). Many large, cross-sectional studies have been conducted on samples drawn from the general population without controlling for access to care (i.e., health insurance coverage). At the same time, ethnicity has been shown to play a role in diabetes complications, but it is not known whether genetics have an impact or whether effects are secondary and associated with access to care – and by extension, socioeconomic status.

A few studies have tried to examine the joint effect of these problems. Karter and colleagues (2002) reported ethnic differences for five major complications observed in a three year longitudinal study of a diabetic population with uniform health care coverage. The patterns of ethnic differences were not consistent across complications and frequently persisted, despite adjustment for a wide range of demographic, socioeconomic, behavioral and clinical factors. The persistence of ethnic disparities after adjustment suggests possible origins related to genetics, unmeasured environmental factors, or a combination of the two (Karter et al., 2002).

Regardless, even people with apparently good access to health services receive care that falls far short of what it could be (Jencks et al., 2003). Healthy People 2010, a document created by the US Department of Health and Human Services confirm wide gaps between public health

performance and actual outcomes based on many quality indicators (Jencks et al., 2003; US Department of Health and Human Services, 2010). In a recent effort to underscore the need for an expanded agenda of public health, a framework was created with the goal of eliminating disparities and improving adult health; it consists of five broad research focus areas: genetic predispositions, behavioral factors, social circumstances, physical environmental factors, and shortfalls in medical care (McGinnis, Williams-Russo, & Knickman, 2002). Such social and environmental pathways must be understood well enough to permit the development of effective chronic disease control strategies for large organizations including employers and government (Ver Ploeg & Perrin, 2004).

Consistent with the framework put forth by McGinnis and colleagues (2002), this study examines baseline predictors of diabetes outcomes among an ethnically diverse working population of diabetics with uniform health care benefits. The goal is to provide a better understanding of risk factors associated with personal characteristics by controlling for access to care in an ethnically diverse sample. It may also yield insights into why some patients are not yet benefiting fully from quality improvement efforts (Jencks et al., 2003; US Department of Health and Human Services, 2010), and inform the design or revision of disease management programs and process of care measures.

3.0 METHODS

3.1 STUDY HYPOTHESIS

The central hypothesis of this study is that quality of diabetes care is associated with reducing the risk of coronary artery disease (CAD), heart failure (HF), Stroke (ischemic or hemorrhagic), and renal disease (RD). The analysis examines the relationships between three quality of diabetes care measures and the risk of macrovascular and microvascular complications in a sample of diabetics employed by a US manufacturer with uniform healthcare benefits and access to healthcare. Measures of quality of diabetes care include A1C tests, lipid tests and urine screening tests for microalbuminuria. While controlling for potential confounding variables (e.g., age, race, gender, income, smoking), the data were analyzed to see if employees who received all three quality of diabetes care measures (QOCM) in the baseline year demonstrated a lower risk for developing any of the four primary complications associated with diabetes over the six-year observation period. Since it was anticipated that individual employee characteristics would impact outcome risk, data on age, gender, ethnicity, marital status, income, insulin use, co-morbidities as measured by health severity risk score, and lifestyle behaviors such as smoking were collected.

3.1.1 Study design

A retrospective cohort study was conducted from January 1, 2003 to December 31, 2009 and included a baseline year (2003) and a six-year observation period (2004 through 2009). The study setting was a US-based, global manufacturing company with approximately 36,000 employees working in 22 states during the years of the study. Most employees held hourly manufacturing jobs, and minorities and women were well represented. Employees selected from a menu of health benefits in terms of costs and deductibles, however only a single Preferred Provider Organization (PPO) network was available to the entire population; Health Maintenance Organization (HMO) alternatives were offered only at a few locations. Because the offered plans were comprehensive in coverage, less than 3% of the employees and their families opted out of health insurance. Eligible participants were employed by the manufacturer in 2001 and 2002 and at least one month in the observation period (2003 through 2009), between 18 and 64 years old, and had submitted a medical claim for one of the following: one hospitalization or emergency room visit, two office visits for diabetes (ICD9 250.XXX) or one prescription for a diabetes medication. Women with gestational diabetes were excluded.

Quality of diabetes care was measured by the assessing the monitoring frequency for all diabetics in 2003, the baseline year. Quality of care benchmarks (i.e., two A1C tests at least 30 days apart in the same year, and annual tests for lipids and microalbuminuria) were set based on relevant performance reporting measures from the American Diabetes Association at the time (Stratton et al., 2003). Diabetics were categorized into two mutually exclusive groups: those who received all of the tests in 2003, and those who did not. The groups, which were large enough to allow for statistical efficiency and power, were compared to assess the differences in risk of developing CAD, HF, Stroke, RD or any of the four complications. The null hypothesis -

that the experimental and control survival curves for each of the four complications were equal - was rejected, with a probability (power) of 0.886 (CAD), 1.000 (HF), 1.000 (Stroke), 0.985 (RD) and 0.976 (any of the four complications). The Type I error probability associated with the test of this null hypothesis was 0.05. Table 1 summarizes the power associated with detecting differences in hazard rates for each complication. Cox proportional hazard regression models were used to assess potential associations between diabetes QOCM and time to complication.

Table 1. Power Associated with Detecting Hazard Rates for Each Complication

HR	Power				
	CAD	CHF	Stroke	Renal	Any 4
1.1	0.21	0.22	0.22	0.22	0.21
1.2	0.58	0.61	0.61	0.61	0.58
1.3	0.86	0.89	0.89	0.89	0.86
1.4	0.97	0.98	0.98	0.98	0.97
1.5	1.00	1.00	1.00	1.00	1.00

3.1.2 Data sources

All data were available as part of a unique academic-corporate partnership that began in 1997 for the purpose of developing and implementing workplace safety and occupational health programs for the manufacturer. The research agreement between the university and the manufacturer allows investigators to extract information from the company's electronic databases which are then de-identified and linked by the university data manager. The databases have been described in greater detail in previous publications (Cullen et al., 2006).

Health data were obtained from the health insurance plan, occupational health medical record reviews, and other employer-managed administrative databases, described below.

1. Health Insurance Claims Database: Investigators receive data on medical and pharmacy claims from a central insurance data processing center each year. The central data processing center receives health insurance data from each third party administrator. Data include ICD-9 codes (US National Center for Health Statistics and the Health Care Financing Administration, 1987) for disease diagnosis and NDCs (National Drug Codes)[1] for prescription information. Data on date of service, provider type, and provider location are also available.
2. Occupational Health Screening: This database provides basic health screening information for employees who participate in fitness-for-duty evaluations at the start of employment and medical surveillance programs. Although the extent of screening varies by job, all employees in this study participated in at least one medical screening program in which smoking status was routinely monitored. Occupational health data were provided to the investigators in one of two ways: an electronic database of data gathered from mandatory health screenings, and data in the employees' occupational health records. Beginning in 2002, an attempt to collect more comprehensive data on employee health risk factors was initiated and a team of investigators began extracting health data from medical departments at individual plants. Data collected included smoking history, cholesterol, blood pressure, height, weight, education status, and marital status.
3. Human Resources: Provided annually, this database contains all employee demographic information, including date of birth, race and gender. Files are created

[1] The National Drug Code Directory can be found at: http://www.accessdata.fda.gov/scripts/cder/ndc/default.cfm .

at the start of employment and document all changes in job title, job grade, job status (active, on leave, retired), job category (hourly or salary), and plant location.

The National Committee for Quality Assurance's (NCQA) Healthcare Effectiveness Data and Information Set (HEDIS) measures for diabetes were obtained from the Health Insurance Data Set. Diagnostic and outcome measures were obtained from inpatient and outpatient claims and pharmacy data provided in the Health Insurance Data Set. Gender, marital status, ethnicity, income, employment status (hourly, salary) were obtained from Human Resources and Occupational Health Screening data sets. These data were used to establish the cohort, tabulate quality indicators (e.g., number of diabetes quality of care tests) and link them to complications from diabetes. Vision claims were not available, therefore claims for routine eye exams and screening for diabetic neuropathy were not usable as quality of diabetes care measures.

Processes of diabetes care were measured by assessing the frequency of monitoring for all diabetics in the baseline year based on a standard of two A1C tests at least thirty days apart and annual tests for lipids and microalbinurea. The A1C tests, lipid test and screening for microalbuminuria were analyzed for collinearity before including them in the model to address their association with complications. Pearson Correlation coefficients ranged from 0.29708 to 0.60935, $p < 0.0001$; lipids and A1C were collinear and could not be evaluated independently. Microalbuminuria was not strongly correlated with A1C and lipids, with coefficients of 0.34193 and 0.29708, respectively. The three measures were combined into a single measure of quality of diabetes care to sharpen the between group contrast and reduce the potential for misclassification associated with simple dichotomization. This approach yielded two groups based on quality of diabetes care that were compared for potential associations with complications (CAD, HF, Stroke or RD).

Sightlines DxCG Risk Solutions Software was used to assign risk scores to the cohort and capture potential illness-related influences on treatment decisions to manage diabetes. Risk adjustment and predictive models enable healthcare organizations and government agencies to analyze, predict and manage risk for their insured populations. DxCG was chosen over the Charlson Index (which was developed specifically for Medicare population) because it differentiates health risk among commercially insured populations and those on Medicare/Medicaid. It uses validated medical and pharmacy classification systems combined with proprietary risk adjustment and predictive models to assign a health severity risk score based on gender, age, race, diagnosis and prescription data that are part of the case mix adjustment model.

Cox proportional hazard regression models were used to assess potential associations between diabetes quality of care measures and time to one of the four complications. Potential confounding risk factors included in all Cox models were sex, age, ethnic group, income, marital status, education, smoking, body mass index, diabetes severity[2] and health severity risk scores.

A sensitivity analysis to assess the effect of continuous optimal care (i.e., at least two A1C tests, one microalbuminuria screen and one lipid test) on adverse outcomes was conducted for 2003 only and the two-year period of 2003 and 2004 in order to determine the appropriateness of the baseline period. The sensitivity analyses were based on a correlation analysis, Kappa statistics and Cox proportional hazard regression models.

[2] Insulin use has been closely associated with duration and severity of diabetes (UKPDS 33, 1998). Diabetes severity was based on an employee's first insulin prescription recorded in the study period (Thompson, 2005).

3.2 ETHICS

Databases were linked by an encrypted unique identifier created by the Yale University Occupational and Environmental Medicine Data Manager to ensure human subject privacy. The Yale University School of Medicine IRB approved this study.

3.3 DIABETES CASE ASCERTAINMENT

Using eligibility criteria outlined in section 3.1.1, diabetes cases were identified in the sample for the baseline year (2003), along with complications occurring anytime during the 72-month observation period (2004 through 2009). If a diabetic had a specific complication in 2001 or 2002, they were excluded from the analysis. Diabetics were identified using ICD-9 codes 250.XX, 3572, 357.2x, 36641, 36201, and 36202. This definition was expansive, in that it included T1DM and T2DM. If an employee had a prescription for a diabetes drug and did not have an ICD-9 code for type, they were coded as T2DM. Diabetics with medical claims for one of the four complications in the baseline year were included in the data set, but were excluded from the analysis for the same complication. For example, if a diabetic had a medical claim with an ICD-9 code for a myocardial infarction in 2003, they were included in the data set but censored from the CAD analysis only. This logic was applied to all complications to eliminate bias from the analysis, since quality of diabetes care in the baseline year was used to predict new complications only. This approach allowed us to include as many individuals in the study as possible. Using this algorithm, data from 1,797 people were included in the analysis (see Figure 1).

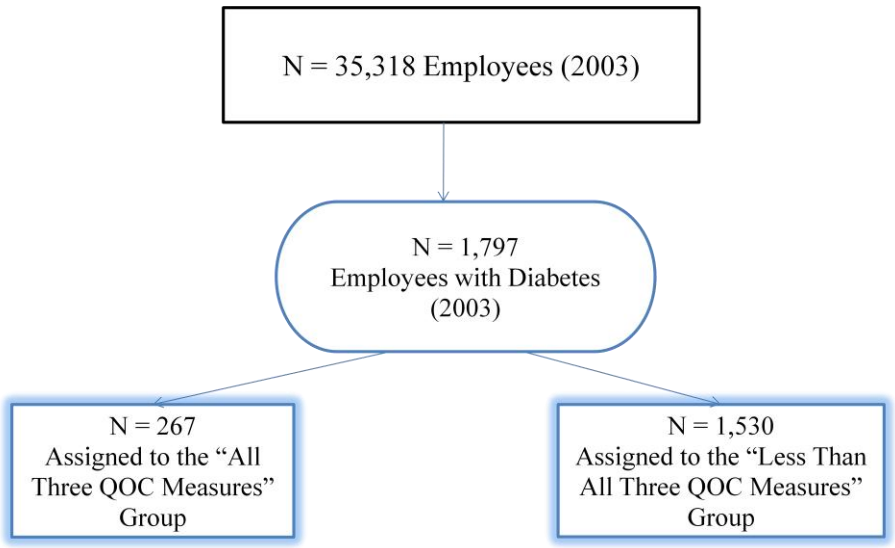


Figure 1. The baseline cohort for the study.

3.4 OUTCOME ASCERTAINMENT

The following ICD-9 codes were used to determine time of onset for any of the four complications: CAD (ICD9 410.XX-414.XX), HF (ICD9 398.91, 428.XX, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93), Stroke (ICD9 430, 431, 432, 433, 434, 435, 436, 437, 438), and RD (ICD9 404.XX, 585, 586 or 403.11, 403.91, 404.12, 404.92, V42.0, V45.1, V56.0, V56.8).

3.4.1 Statistical analysis

Hazard ratios for outcomes (CAD, HF, Stroke, RD) were calculated for quality of diabetes care (exposures) and covariates. The Kaplan-Meier method was used to identify crude time-to-event models for the associations between exposures and outcome variables. Time-to-event methods

were used for all primary analyses. For a given outcome, the time-to-event was defined as the number of months from the start of the observation period (January 1, 2004) to the first medical claim for a complication. Diabetics who no longer received employer-provided health benefits were censored at the time of the last medical claim. Tests for all time-dependent variables were not significant, either individually or collectively. The assumption of proportional hazards was visually examined, and there was not enough evidence to reject proportionality. Thus, the assumption of proportionality for this model was satisfied.

Time-dependent Cox proportional hazard models were used to evaluate bivariate and multivariate models, which enabled time-to-outcome assessment and risk adjustment based on socioeconomic and lifestyle risk factors (gender, age, race, marital status, salary, and smoking), co-morbidities (health severity risk scores), and severity of diabetes (insulin, no-insulin). Hazard ratios for primary outcome comparisons were calculated based on Cox proportional hazard analyses stratified by hourly, salary, gender and insulin use. In addition, Kappa statistics, correlation analyses and Cox proportional hazard analyses were used to assess outcome differences based on two years (2003 and 2004) of continuous QOCM. All analyses were conducted using SAS software version 9.2.

4.0 RESULTS

4.1 BASELINE CHARACTERISTICS

A total of 1,797 patients were included in the analysis. The base model was specified with demographics and then groups of related, potentially explanatory variables such as SES, modifiable risks and clinical characteristics were added to the demographic model. First, SES indicators such as individual income, job status (hourly or salary), and marital status were included, followed by smoking status as a modifiable risk. Clinical characteristics specific to diabetes, such as insulin use and health severity risk score, were then added as measures of co-morbidities. Finally, a fully-adjusted model was used to assess the combined explanatory effects for all measured factors.

Baseline characteristics of the sample are presented in Table 2. The cohort consisted primarily of Caucasian (63.7%), male (85.8%), married (76.4%) hourly employees (75.7%), a significant number of whom earned less than $35,423 per year (27.2%). More than half (55.1%) were between the ages of 18 and 51. The mean age for the total population was 49.0 years (sd = 8.4). Smoking data was reported as never (14.4%), past/current (17.3%) and unknown (68.3%); smoking rates were slightly lower than for the general US population of working men and women (21%) (Centers for Disease Control and Prevention, 2008; Cowie, Rust, Byrd-Holt, & Eberhardt, 2003). As a measure of diabetes severity, 23.1% of the population had insulin

prescriptions during the baseline year. Health severity risk scores were used to assess co-morbidities, with 76.1% of the cohort receiving a score of 2.1 or lower. For the quality of diabetes care measures, 61.8 % of the total population was tested in the baseline year, with 43.0% receiving at least two A1C tests and 24.0% receiving tests for microalbuminuria.

Table 2. Demographic Characteristics (2003)

Characteristic	Diabetics (N = 1797)	
Age	n	%
18 - 45	522	29.0
46 - 51	469	26.1
52 - 56	469	26.1
57- 64	337	18.8
Gender		
Male	1494	83.1
Female	303	16.9
Race		
White	1244	69.2
Black	346	19.3
Hispanic	166	9.2
Other	41	2.3
Marital Status/Dependents*		
Married (spouse on health insurance)	1333	74.2
Compensation		
Hourly	1361	75.7
Salary	436	24.3
Wage		
Quartile 1 (< $35,423)	488	27.2
Quartile 2 ($35,424 - $44,743)	435	24.2
Quartile 3 ($44,744 - $56,903)	444	24.7
Quartile 4 (> $56,903)	430	23.9
Smoking		
Never	258	14.4
Past/Current	311	17.3
Unknown	1228	68.3
Insulin	361	20.1
Health Severity Risk Score		
Quartile 1 (≤ 1.0)	451	25.1
Quartile 2 (1.0 - 1.4)	448	24.9
Quartile 3 (1.4 - 2.1)	451	25.1
Quartile 4 (≥ 2.1)	447	24.9
Quality of Care Measures		
A1C (1 tests)	1214	67.6
A1C (2 tests)	773	43.0
Microalbuminuria	431	24.0
Lipids	1110	61.8

Table 2 (continued)

* determined from health insurance eligibility file

4.2 COMPLICATIONS IN THE COHORT

In total, 24% (n = 366) of the cohort reported a claim for one of the four complications over the six-year observation period with a mean time-to-complication of 29.1 months. The most frequent complication in the cohort was CAD (16.9%, n = 267) with a mean time-to-complication of 26.6 months. RD (4.9%, n = 86) was the least frequent complication in the cohort, and had the longest mean time-to-complication of 38.1 months.

Table 3. Complications in the Cohort (2004-2009)

Complication	Diabetics (N = 1797)		Mean Time-to- Complication (in months)
	n	%	
CAD	267	16.9	26.6
HF	102	5.8	29.7
Stroke	152	8.7	33.1
RD	86	4.9	38.1
1 or more of the above	366	24.0	29.1

4.3 QUALITY OF CARE MEASURES

At baseline, the cohort receiving all three quality of diabetes care measures (QOCM) was smaller (n = 267) than the comparison group (n = 1,530). Statistics for QOCM are shown in Table 4. Chi square statistics were performed to assess differences between the two groups. Despite the sample size differences in the cohorts, there were no statistically significant differences between

the two study groups during the baseline period (2003) for demographic, SES or modifiable risk variables, with the exception of insulin prescriptions in the group that received all three QOCM versus the group that received less than all three QOCM, which were 27.7%, n = 74 and 18.8%, n = 287, respectively, with p = 0.0007. Health severity risk scores were also significantly different between the two groups (p = 0.0429).

Table 4. Statistics for QOCM during the Baseline Period (2003)

Employees with Diabetes (N = 1797)	All 3 QOCM (n = 267)		< 3 QOCM (n = 1530)		p-value
Characteristic	n	%	n	%	
Age					0.2973
18 - 45	75	28.1	447	29.2	
46 - 51	74	27.7	395	25.8	
52 - 56	70	26.2	399	26.1	
57- 64	48	18.0	289	18.9	
Gender					0.2137
Male	229	85.8	1265	82.7	
Female	38	14.2	265	17.3	
Race					0.1525
White	170	63.7	1074	70.2	
Black	59	22.1	287	18.8	
Hispanic	32	12.0	134	8.8	
Other	6	2.2	35	2.3	
Marital Status*					
Married	204	76.4	1129	73.8	0.3679
Compensation					0.3679
Hourly	186	69.7	1175	76.8	
Salary	81	30.3	355	23.2	
Wage					0.864
Quartile 1 (< $35,423)	67	25.1	421	27.5	
Quartile 2 ($35,424 - $44,743)	65	24.3	370	24.2	
Quartile 3 ($44,744 - $56,903)	69	25.8	375	24.5	
Quartile 4 (> $56,903)	66	24.7	364	23.8	
Smoking					0.2495
Never	32	12.0	226	14.8	
Past/Current	41	15.4	270	17.6	
Unknown	194	72.7	1034	67.6	
Insulin	74	27.7	287	18.8	0.0007
Health Severity Risk Score					0.0429
Quartile 1 (≤ 1.0)	50	18.7	401	26.2	
Quartile 2 (1.0 - 1.4)	67	25.1	381	24.9	
Quartile 3 (1.4 - 2.1)	71	26.6	380	24.8	
Quartile 4 (≥ 2.1)	79	29.6	368	24.1	

*determined from health insurance eligibility files.

4.4 CENSORED DATA

Of the 901 records censored during the observation period (January 1, 2004 through December 31, 2009), 647 were due to retirement, layoff or termination. There were 14 deaths, and 16 diabetics went on long term disability, but death certificates and detailed disability information were unavailable for analysis. Chi square statistics were performed to assess differences between the two groups. Since most data were censored based on retirement, layoff or termination, the statistically significant differences found for age ($p < 0.0001$) and salary ($p = 0.0001$) were expected. Differences in race, marital status, compensation (salary or hourly), insulin use and health severity risk score were not significant. Most importantly, there was no evidence that those whose data were censored had different rates of receiving all three QOCM than those whose data were not censored, suggesting censorship as an unlikely source of importance bias.

Table 5. Data Censorship Statistics

Characteristic	Censored (n = 901)		Not Censored (n = 625)		p-value
	n	%	n	%	
Age					<.0.0001
18 - 45	322	35.7	165	26.4	
46 - 51	205	22.8	202	32.3	
52 - 56	207	23.0	163	26.1	
57- 64	167	18.5	95	15.2	
Gender					0.3267
Male	738	81.9	524	83.8	
Female	163	18.1	101	16.2	
Race					0.4363
White	603	66.9	433	69.3	
Black	190	21.1	111	17.8	
Hispanic	85	9.4	65	10.4	
Other	23	2.6	16	2.6	
Marital Status*					
Married	644	71.5	468	74.9	0.1414
Compensation					0.514
Hourly	673	74.7	476	76.2	
Salary	228	25.3	149	23.8	

Table 5 (continued)

Wage					<.0001
Quartile 1 (< $35,423)	283	31.4	127	20.3	
Quartile 2 ($35,424 - $44,743)	229	25.4	144	23.0	
Quartile 3 ($44,744 - $56,903)	188	20.9	189	30.2	
Quartile 4 (> $56,903)	201	22.3	165	26.4	
Smoking					<.0001
Never	111	12.3	117	18.7	
Past/Current	117	13.0	138	22.1	
Unknown	673	74.7	370	59.2	
Insulin	167	18.5	133	21.3	0.1846
Health Severity Risk Score					0.1161
Quartile 1 (≤ 1.0)	261	29.0	174	27.8	
Quartile 2 (1.0 - 1.4)	267	29.6	156	25.0	
Quartile 3 (1.4 - 2.1)	216	24.0	171	27.4	
Quartile 4 (≥ 2.1)	157	17.4	124	19.8	
Quality of Care Measures					
A1C (1 tests)	592	65.7	429	68.6	0.2308
A1C (2 tests)	375	41.6	274	43.8	0.3884
Microalbuminuria	222	24.6	160	25.6	0.6701
Lipids	532	59.0	387	61.9	0.2592

* determined from health insurance eligibility files

4.5 COMPLICATIONS

4.5.1 Coronary artery disease (CAD)

The most frequent complication in the cohort was CAD (16.9%, n = 267) with a mean time-to-complication of 26.6 months. The hazard rate (HR 0.70, 95% CI [0.49 - 1.02], p = 0.0635) was lower for diabetics with at least one claim for CAD who received all three QOCM in the baseline year relative to diabetics with CAD who did not receive all three QOCM in the baseline year. The difference was borderline significant.

Certain diabetic characteristics were more likely to be associated with developing CAD as a complication of diabetes in the multivariate model (see Table 6). Males (HR 1.72, 95% CI

[1.15 - 2.56], p = 0.008) were significantly more likely to develop CAD than females. Older people (aged 46 to 51 years) were also at increased risk for CAD (HR 1.81, 95% CI [1.24 - 2.54], p = 0.002). Smoking, either in the past or during the study, also increased the risk for CAD, with a borderline significant hazard rate of 1.47 (95% CI [0.97 - 2.21], p = 0.0676). In addition, a health severity risk score greater than 2.1 was associated with a statistically significant increased risk of CAD (HR 2.17, 95% CI [1.47 - 2.19], p < 0.0001). The health severity risk score includes age, gender and comorbidities, and therefore may cause an underestimation of associations with co-morbidities.

Table 6. Multivariate Associations with CAD (2004-2009)

Characteristic	All (N = 1580)		Bivariate				Multivariate (demographics, lifestyle, QOC, and HSRS)			
	n	%	HR	95% CI		p-value	HR	95% CI		p-value
Age										
18 - 45	497	31.5	1.00	reference			1.00	reference		
46 - 51	418	26.5	1.99	1.39	2.84	0.0002	1.81	1.24	2.64	0.002
52 - 56	386	24.4	2.26	1.58	3.23	<.0001	1.85	1.25	2.74	0.0022
57- 64	279	17.7	3.30	2.25	4.84	<.0001	2.61	1.70	4.00	<.0001
Gender										
Male	1305	82.6	1.55	1.07	2.24	0.0205	1.72	1.15	2.56	0.008
Race										
White	1074	68.0	1.00	reference						
Black	313	19.8	0.85	0.62	1.17	0.3246	0.92	0.66	1.27	0.6014
Hispanic	153	9.7	0.82	0.54	1.25	0.3566	0.87	0.57	1.33	0.5195
Other	40	2.5	1.21	0.57	2.56	0.6278	1.14	0.53	2.45	0.729
Marital Status										
Married	1151	72.8	1.13	0.86	1.49	0.3908	0.92	0.69	1.24	0.5921
Compensation										
Hourly	1182	74.8	1.25	0.93	1.68	0.1398	1.24	0.88	1.73	0.2173
Wage										
Quartile 1 (< $35,423)	425	26.9	1.00	reference			1.00	reference		
Quartile 2 ($35,424 - $44,743)	382	24.2	1.37	0.97	1.93	0.0754	1.19	0.83	1.70	0.3552
Quartile 3 ($44,744 - $56,903)	392	24.8	1.14	0.80	1.61	0.4719	0.97	0.66	1.42	0.8778
Quartile 4 (> $56,903)	381	24.1	1.15	0.81	1.64	0.4412	0.96	0.63	1.46	0.8499
Smoking										
Never	235	14.9	1.00	reference			1.00	reference		
Past/Current	265	16.8	1.60	1.07	2.41	0.0229	1.47	0.97	2.21	0.0676
Unknown	1080	68.4	1.15	0.81	1.64	0.4276	1.19	0.82	1.71	0.3669
Insulin	311	19.7	1.15	0.86	1.54	0.343	1.14	0.84	1.54	0.406
Health Severity Risk Score										

Table 6 (continued)

Quartile 1 (≤ 1.0)	438	27.7	1.00	reference			1.00	reference		
Quartile 2 (1.0 - 1.4)	424	26.8	1.38	0.96	2.00	0.0833	1.17	0.79	1.72	0.426
Quartile 3 (1.4 - 2.1)	399	25.3	1.62	1.14	2.31	0.0075	1.28	0.87	1.89	0.2134
Quartile 4 (≥ 2.1)	319	20.2	2.76	1.96	3.88	<.0001	2.17	1.47	3.19	<.0001
Quality of Care Measures (2003)										
All 3 QOCM*	235	14.9	0.76	0.53	1.10	0.1424	0.70	0.49	1.02	0.0635

* 2 A1C measurements, 1 microalbuminuria test, and 1 lipid test in 2003

4.5.2 Heart failure (HF)

During the six-year observation period, 102 diabetics had at least one medical claim for HF. HF was the third most frequent complication in the cohort (5.8%), with a mean time-to-complication of 29.7 months. The hazard rate for diabetics who submitted at least one medical claim for HF was lower for those who received all three QOCM in the baseline year (HR 0.39, 95% CI [0.19 - 0.81], p = 0.0118) compared to diabetics who received less than all three QOCM.

Certain covariates were more likely to be associated with medical claims for HF as a complication of diabetes in the multivariate model (see Table 7). Although rates varied modestly among groups by race and gender, neither was statistically significant. Hazard rates increased along with age, which was borderline significant for diabetics aged 46 to 51 years (p = 0.0513) and statistically significant for diabetics aged 52 to 56 years (p = 0.0013) and 57 to 64 years (p < 0.0001). Smoking, both in the past and during the study, was associated with a more than two-fold risk for submitting a claim for HF (HR 2.21, 95% CI [1.06 - 4.62], p = 0.00353). Although increasing age and smoking are known risk factors for HF among diabetics (Cowie et al., 2003), it has been cited elsewhere that younger age groups are also at increased risk (Nichols, Gullion, Koro, Ephross, & Brown, 2004).

Health severity risk scores of 2.1 or greater were associated with higher hazard rates than those with lower scores (HR 2.05, 95% CI [1.04 - 4.03], p = 0.038). Ischemic heart disease is often comorbid with diabetes, and is an important predictor of HF in diabetics, especially among those who use insulin (Nichols et al., 2004). However, insulin use was not associated with HF risk in this cohort. All other associations were insignificant.

Table 7. Multivariate Associations with HF (2004-2009)

Characteristic	All (N = 1765)		Bivariate				Multivariate (demographics, lifestyle, QOC, and HSRS)			
Age	n	%	HR	95% CI		p-value	HR	95% CI		p-value
18 - 45	518	29.3	1.00	reference			1.00	reference		
46 - 51	462	26.2	2.40	1.14	5.03	0.0212	2.15	1.00	4.65	0.0513
52 - 56	456	25.8	4.25	2.11	8.57	<.0001	3.42	1.61	7.25	0.0013
57- 64	329	18.6	8.47	4.16	17.24	<.0001	6.44	2.96	14.01	<.0001
Gender										
Male	1467	83.1	0.87	0.53	1.43	0.5863	1.01	0.57	1.79	0.9641
Race										
White	1220	69.1	1.00	reference						
Black	340	19.3	1.34	0.84	2.12	0.2179	1.50	0.93	2.41	0.0961
Hispanic	165	9.3	1.02	0.53	1.99	0.949	1.14	0.58	2.25	0.6966
Other	40	2.3	0.54	0.08	3.89	0.5403	0.45	0.06	3.28	0.4317
Marital Status										
Married	1308	74.1	1.16	0.73	1.85	0.5312	1.05	0.64	1.73	0.8529
Compensation										
Hourly	1335	75.6	1.31	0.80	2.13	0.2845	1.19	0.68	2.07	0.5503
Wage										
Quartile 1 (< $35,423)	480	27.2	1.00	reference			1.00	reference		
Quartile 2 ($35,424 - $44,743)	424	24.0	1.34	0.77	2.31	0.3015	1.22	0.69	2.18	0.4952
Quartile 3 ($44,744 - $56,903)	438	24.8	1.02	0.58	1.79	0.9559	1.01	0.54	1.90	0.9682
Quartile 4 (> $56,903)	423	24.0	1.13	0.64	1.99	0.6797	1.05	0.53	2.07	0.8913
Smoking										
Never	255	14.4	1.00	reference			1.00	reference		
Past/Current	305	17.3	2.42	1.17	5.01	0.0177	2.21	1.06	4.62	0.0353
Unknown	1205	68.3	1.74	0.89	3.38	0.105	1.65	0.82	3.31	0.1576
Insulin	349	19.8	1.46	0.94	2.28	0.0962	1.54	0.96	2.46	0.0707
Health Severity Risk Score										
Quartile 1 (≤ 1.0)	451	25.6	1.00	reference			1.00	reference		
Quartile 2 (1.0 - 1.4)	447	25.3	1.64	0.86	3.14	0.1361	1.16	0.58	2.35	0.6729
Quartile 3 (1.4 - 2.1)	449	25.4	1.95	1.06	3.60	0.032	1.14	0.57	2.29	0.7075
Quartile 4 (≥ 2.1)	418	23.7	3.65	2.06	6.46	<.0001	2.05	1.04	4.03	0.038
Quality of Care Measures (2003)										
All 3 QOCM*	263	14.9	0.47	0.23	0.96	0.0377	0.39	0.19	0.81	0.0117

* 2 A1C measurements, 1 microalbuminuria test, and 1 lipid test in 2003

4.5.3 Stroke

During the six-year observation period, 152 diabetics submitted at least one medical claim for stroke. Stroke was the second most frequent complication in the cohort (8.7%), with a mean time-to-complication of 33.1 months. The risk of submitting a medical claim for stroke was 0.63 (HR 0.63, 95% CI [0.38 – 1.07], p = 0.0891) for diabetics receiving all three QOCM in the baseline year compared to diabetics who received less than all three QOCM in the baseline year.

Certain covariates were more likely to be associated with having a medical claim for stroke as a complication of diabetes in the multivariate model (see Table 8). Males (HR 0.77, 95% CI [0.50 - 1.21], p = 0.261) were less likely to have strokes than females, but the difference was not significant. The hazard rate for Hispanics was lower relative to blacks and whites (HR 0.55, 95% CI [0.28 - 1.08], p = 0.083) with borderline significance. Similarly, Karter (2008) reported a lower hazard rate for Latinos (HR 0.72, 95% CI [0.59 - 0.88], p < 0.002) relative to whites and blacks. Increasing age was significantly associated with increased risk for stroke for 52 to 56 year olds (HR 2.95, 95% CI [1.69 - 5.15], p = 0.0001). Smoking, either in the past or during the study, also was significantly associated with increased risk of stroke (HR 2.21, 95% CI [1.06 - 4.62], p = 0.00353). Increasing age and smoking are known risk factors for stroke among diabetics (Rodbard et al., 2007). A health severity risk score of 2.1 or higher was associated with a significantly increased risk for stroke compared to those with lower scores (HR 2.04, 95% CI [1.18 - 3.04], p = 0.011). Consistent with observations reported by Libby and colleagues (2005), neither insulin use nor smoking was significantly associated with risk of stroke.

Table 8. Multivariate Associations with Stroke (2004-2009)

Characteristic	All (N = 1751)		Bivariate				Multivariate (demographics, lifestyle, QOC, and HSRS)			
Age	n	%	HR	95% CI		p-value	HR	95% CI		p-value
18 - 45	517	29.5	1.00	reference			1.00	reference		
46 - 51	457	26.1	1.80	1.02	3.16	0.042	1.53	0.85	2.75	0.1545
52 - 56	453	25.9	3.67	2.19	6.16	<.0001	2.95	1.69	5.15	0.0001
57- 64	324	18.5	6.21	3.60	10.72	<.0001	4.65	2.57	8.44	<0.0001
Gender										
Male	1453	83.0	0.71	0.49	1.05	0.0875	0.77	0.50	1.21	0.2609
Race										
White	1210	69.1	1.00	reference			1.00	reference		
Black	340	19.4	0.78	0.51	1.20	0.2621	0.81	0.52	1.25	0.3304
Hispanic	162	9.3	0.51	0.26	1.00	0.0508	0.55	0.28	1.08	0.0833
Other	39	2.2	0.31	0.04	2.18	0.236	0.23	0.03	1.66	0.1452
Marital Status										
Married	1295	74.0	0.98	0.68	1.41	0.9231	0.88	0.60	1.31	0.543
Compensation										
Hourly	1332	76.1	1.13	0.77	1.67	0.5231	1.27	0.81	1.98	0.2988
Wage										
Quartile 1 (< $35,423)	474	27.1	1.00	reference			1.00	reference		
Quartile 2 ($35,424 - $44,743)	427	24.4	0.81	0.51	1.31	0.3925	0.85	0.52	1.41	0.5351
Quartile 3 ($44,744 - $56,903)	432	24.7	0.93	0.59	1.45	0.7364	1.15	0.70	1.89	0.5907
Quartile 4 (> $56,903)	418	23.9	1.12	0.72	1.73	0.6123	1.28	0.74	2.21	0.3713
Smoking										
Never	253	14.4	1.00	reference			1.00	reference		
Past/Current	301	17.2	1.61	0.91	2.83	0.0997	1.35	0.76	2.38	0.3043
Unknown	1197	68.4	1.46	0.90	2.40	0.1289	1.39	0.83	2.32	0.2171
Insulin	354	20.2	1.06	0.71	1.57	0.7779	1.04	0.69	1.57	0.8559
Health Severity Risk Score										
Quartile 1 (≤ 1.0)	447	25.5	1.00	reference			1.00	reference		
Quartile 2 (1.0 - 1.4)	448	25.6	1.29	0.75	2.22	0.366	0.94	0.52	1.69	0.8221
Quartile 3 (1.4 - 2.1)	439	25.1	2.26	1.41	3.63	0.0007	1.46	0.85	2.51	0.1704
Quartile 4 (≥ 2.1)	417	23.8	3.30	2.08	5.23	<.0001	2.04	1.18	3.52	0.0105
Quality of Care Measures (2003)										
All 3 QOCM*	263	15.0	0.63	0.37	1.05	0.0785	0.63	0.38	1.07	0.0891

* 2 A1C measurements, 1 microalbuminuria test, and 1 lipid test in 2003

4.5.4 Renal disease (RD)

During the six-year observation period, 4.9% (n = 86) of the cohort submitted at least one medical claim for RD, with a mean time-to-complication of 38.1 months. This group had the longest time-to-complication during the six years of observation. The hazard rate was lower for diabetics who received all three QOCM in the baseline year (HR 0.48, 95% CI [0.24 - 0.95], p =

0.0339) compared to diabetics who received less than all three QOCM. The difference between the two groups is statistically significant.

Other covariates were more likely to be associated with medical claims for RD as a complication of diabetes in the multivariate model (see Table 9). There was no statistical association observed in the bivariate and multivariate models between males (p = 0.8612) and females (p = 0.5447). Increased hazard rates were associated with increasing age; hazard rates were 2.71 for 52 to 56 year olds (95% CI [1.31 - 5.62], p = 0.0073) and 4.19 for 57 to 64 year olds (95% CI [1.89 - 9.26], p = 0.0004). Relative to whites, blacks (HR 1.77, 95% CI [1.06 - 2.97], p = 0.0295) had a statistically significant higher risk. A health severity risk score of 2.1 or greater was associated with a higher hazard rate than those with lower scores (HR 2.16, 95% CI [1.06 - 4.41], p = 0.0349), and insulin use was associated with a significantly increased risk of RD (p = 0.0001).

Table 9. Multivariate Associations with RD (2004-2009)

Characteristic	All (N = 1785)		Bivariate				Multivariate (demographics, lifestyle, QOCM, and HSRS)			
Age	n	%	HR	95% CI		p-value	HR	95% CI		p-value
18 - 45	521	29.2	1.00	reference			1.00	reference		
46 - 51	467	26.2	1.75	0.86	3.55	0.1234	1.70	0.80	3.58	0.1657
52 - 56	467	26.2	3.15	1.62	6.11	0.0007	2.71	1.31	5.62	0.0073
57- 64	330	18.5	5.19	2.54	10.59	<.0001	4.19	1.89	9.26	0.0004
Gender										
Male	1486	83.2	0.95	0.55	1.66	0.8612	1.22	0.65	2.29	0.5447
Race										
White	1234	69.1	1.00	reference			1.00	reference		
Black	344	19.3	1.47	0.90	2.42	0.1268	1.77	1.06	2.97	0.0295
Hispanic	166	9.3	1.39	0.73	2.66	0.3197	1.60	0.82	3.11	0.1693
Other	41	2.3	0.00	0.00	.	0.9798	0.00	0.00	.	0.9791
Marital Status										
Married	1324	74.2	1.44	0.84	2.48	0.1885	1.27	0.71	2.27	0.4209
Compensation										
Hourly	1354	75.9	0.86	0.53	1.38	0.526	0.76	0.44	1.33	0.3395
Wage										
Quartile 1 (< $35,423)	484	27.1	1.00	reference			1.00	reference		

Table 9 (continued)

Quartile 2 ($35,424 - $44,743)	434	24.3	1.08	0.59	1.99	0.8059	0.99	0.52	1.87	0.9687
Quartile 3 ($44,744 - $56,903)	442	24.8	1.09	0.60	1.96	0.7834	1.19	0.62	2.28	0.6063
Quartile 4 (> $56,903)	425	23.8	0.98	0.53	1.83	0.9541	0.84	0.40	1.76	0.6515
Smoking										
Never	255	14.3	1.00	reference			1.00	reference		
Past/Current	310	17.4	1.98	0.85	4.58	0.1123	2.01	0.86	4.69	0.1074
Unknown	1220	68.3	2.25	1.07	4.72	0.0316	2.22	1.03	4.77	0.0411
Insulin	357	20.0	2.69	1.74	4.15	<.0001	2.52	1.58	4.03	0.0001
Health Severity Risk Score										
Quartile 1 (≤ 1.0)	450	25.2	1.00	reference			1.00	reference		
Quartile 2 (1.0 - 1.4)	448	25.1	1.38	0.68	2.81	0.3766	0.95	0.44	2.05	0.8966
Quartile 3 (1.4 - 2.1)	451	25.3	1.38	0.70	2.75	0.3533	0.82	0.38	1.79	0.6243
Quartile 4 (≥ 2.1)	436	24.4	4.01	2.21	7.28	<.0001	2.16	1.06	4.41	0.0349
Quality of Care Measures (2003)										
All 3 QOCM*	266	14.9	0.71	0.37	1.38	0.3119	0.48	0.24	0.95	0.0339

* 2 A1C measurements, 1 microalbuminuria test, and 1 lipid test in 2003

4.5.5 Any of the four complications

During the six-year observation period, a total of 366 diabetics (24%, N = 1,797) had medical claims for at least one of the four complications with a mean time-to-complication of 29.1 months (see Table 10). The hazard rate for submitting a medical claim for any of the four complications was significantly lower for those receiving all three QOCM (HR 0.66, 95% CI [0.48 - 0.91], p = 0.0101).

Increasing age was significantly associated with a higher risk for complications. Health severity risk scores of 2.1 or higher were significantly associated with higher hazard rates than lower scores (HR 1.91, 95% CI [1.36 - 2.68], p = 0.0002). There is also evidence that smoking, independent of the other factors, contributed to risk (HR 1.44, 95% CI [1.01 – 2.07], p = 0.0468). Differences in all other covariates were not statistically significant.

Table 10. Multivariate Associations with Any of the Four Complications (2004-2009)

Characteristic	All (N = 1526)		Bivariate				Multivariate (demographics, lifestyle, QOCM, and HSRS)			
Age	n	%	HR	95% CI		p-value	HR	95% CI		p-value
18 - 45	487	31.9	1.00	reference			1.00	reference		
46 - 51	407	26.7	2.04	1.50	2.79	<.0001	1.88	1.36	2.61	0.0001
52 - 56	370	24.2	2.43	1.78	3.32	<.0001	2.06	1.47	2.89	<.0001
57- 64	262	17.2	3.89	2.80	5.41	<.0001	3.09	2.15	4.46	<.0001
Gender										
Male	1262	82.7	1.09	0.82	1.44	0.5437	1.18	0.87	1.61	0.2867
Race										
White	1036	67.9	1.00	reference			reference			
Black	301	19.7	1.00	0.78	1.30	0.9791	1.05	0.80	1.36	0.7457
Hispanic	150	9.8	0.80	0.56	1.16	0.2411	0.86	0.60	1.25	0.4369
Other	39	2.6	0.90	0.42	1.90	0.7715	0.83	0.39	1.77	0.6282
Marital Status										
Married	1112	72.9	1.12	0.89	1.43	0.3346	0.99	0.77	1.28	0.9475
Compensation										
Hourly	1149	75.3	1.09	0.85	1.39	0.4959	1.09	0.82	1.44	0.5436
Wage										
Quartile 1 (< $35,423)	410	26.9	1.00	reference			1.00	reference		
Quartile 2 ($35,424 - $44,743)	373	24.4	1.10	0.81	1.48	0.5484	1.00	0.73	1.36	0.9988
Quartile 3 ($44,744 - $56,903)	377	24.7	1.04	0.78	1.39	0.7946	0.96	0.70	1.32	0.8029
Quartile 4 (> $56,903)	366	24.0	1.13	0.84	1.51	0.43	0.98	0.69	1.39	0.9029
Smoking										
Never	228	14.9	1.00	reference			1.00	reference		
Past/Current	255	16.7	1.55	1.08	2.21	0.0173	1.44	1.01	2.07	0.0468
Unknown	1043	68.3	1.31	0.97	1.78	0.0817	1.30	0.94	1.79	0.1118
Insulin	300	19.7	1.16	0.90	1.49	0.2476	1.20	0.92	1.55	0.1797
Health Severity Risk Score										
Quartile 1 (≤1.0)	435	28.5	1.00	reference			1.00	reference		
Quartile 2 (1.0 - 1.4)	423	27.7	1.53	1.13	2.08	0.0068	1.20	0.87	1.66	0.2731
Quartile 3 (1.4 - 2.1)	387	25.4	1.93	1.44	2.60	<.0001	1.38	0.99	1.91	0.0541
Quartile 4 (≥ 2.1)	281	18.4	2.70	2.00	3.66	<.0001	1.91	1.36	2.68	0.0002
Quality of Care Measures (2003)										
All 3 QOCM *	232	15.2	0.72	0.53	0.99	0.041	0.66	0.48	0.91	0.0101

* 2 A1c measurements, 1 microalbuminuria test, and 1 lipid test in 2003

4.6 TIME TREND ANALYSES

The Kaplan-Meier estimates of cumulative hazards for all complications indicate that differences between the two quality of diabetes care groups began to develop early in the observation period

(see Figure 2 and Table 11). The cumulative hazards for CAD begin to diverge at three months, converge at 32 months and then diverge again at 37 months, continuing through the remainder of the observation period. For HF, the curves separate soon after the baseline period at four months and show increasing benefits associated with quality of diabetes care continuing through the end of the observation period. For Stroke, the cumulative hazard function diverges at four months and continues to demonstrate benefits through the six-year observation period. For RD, the cumulative hazard function diverges at 27 months, narrows at 61 months and then diverges for the remainder of the observation period. For any of the four complications, the treatment groups begin to diverge at two months with a narrowing at 31 months. However, the divergence persists through the observation period, showing the benefits associated with higher quality of diabetes care.

Adjusted models indicate that diabetics who received all three QOCM experienced a significantly lower risk for HF (HR 0.39, 95% CI [0.19 - 0.81], p = 0.0117). Based on the adjusted multivariate analysis, diabetics who received all three QOCM also experienced a significantly delayed onset of RD (HR 0.48, 95% CI [0.24 - 0.95], p = 0.0339); in fact, diabetics who received all three QOCM experienced delayed onset for any of the four complications compared to the other group (HR 0.66, 95% CI [0.48 - 0.91], p = 0.0101). Hazard rates for the cohort are presented in Table 11.

Table 11. Cox Proportional Hazard Regression Model for the Effect of Receiving All Three QOCM* on Complications (2003)

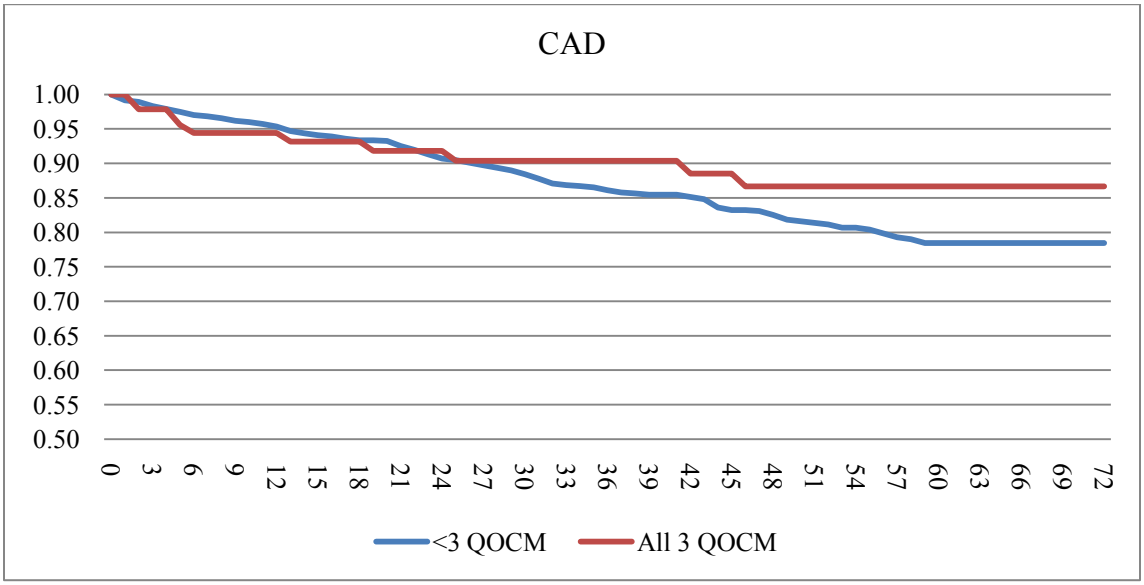
Complication	Unadjusted HR				Adjusted HR**			
	HR	95% CI		p-value	HR	95% CI		p-value
CAD (n = 1580)	0.76	0.53	1.10	0.1424	0.70	0.49	1.02	0.0635
HF (n = 1765)	0.47	0.23	0.96	0.0377	0.39	0.19	0.81	0.0117
Stroke (n = 1751)	0.63	0.37	1.05	0.0785	0.63	0.38	1.07	0.0891
RD (n = 1785)	0.71	0.37	1.38	0.3119	0.48	0.24	0.95	0.0339

Table 11 (continued)

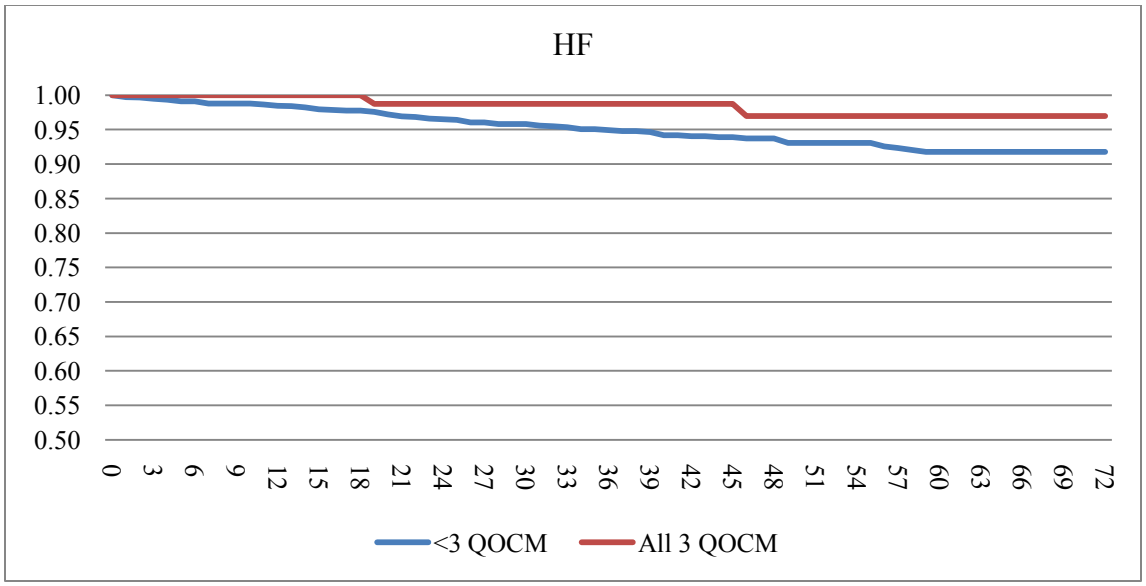
Any of the 4 (n = 1526)	0.72	0.53	0.99	0.041	0.66	0.48	0.91	0.0101

* 2 A1C measurements, 1 microalbuminuria test, and 1 lipid test in 2003
** Demographics, modifiable risks, clinical measures of risk

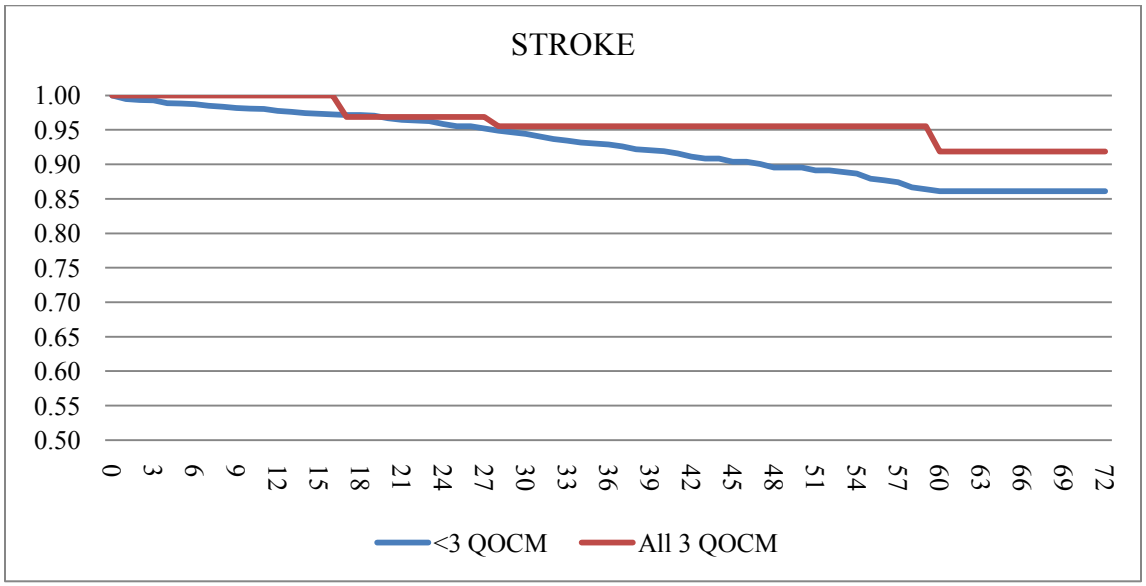
Kaplan-Meier estimates of cumulative hazard ratios for complications are presented in Figure 2 (a-e). All hazard ratios were adjusted based on demographic characteristics, lifestyle factors, health severity risk scores and disease severity based on insulin use.



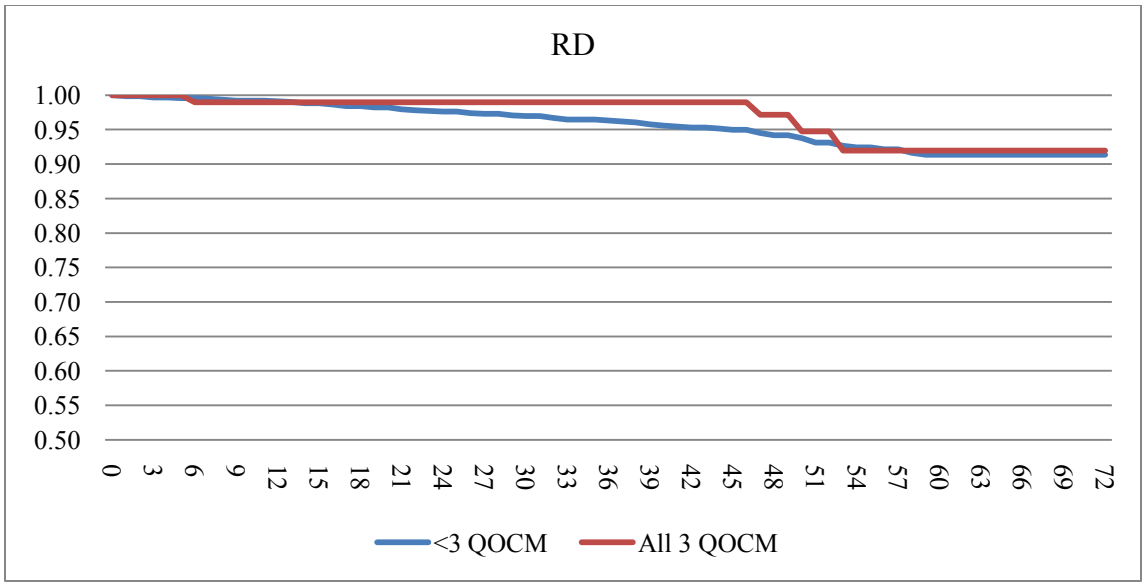
(a) CAD (n = 1,580, HR .70, 95% [CI .49 - 1.02], p = 0.0635)



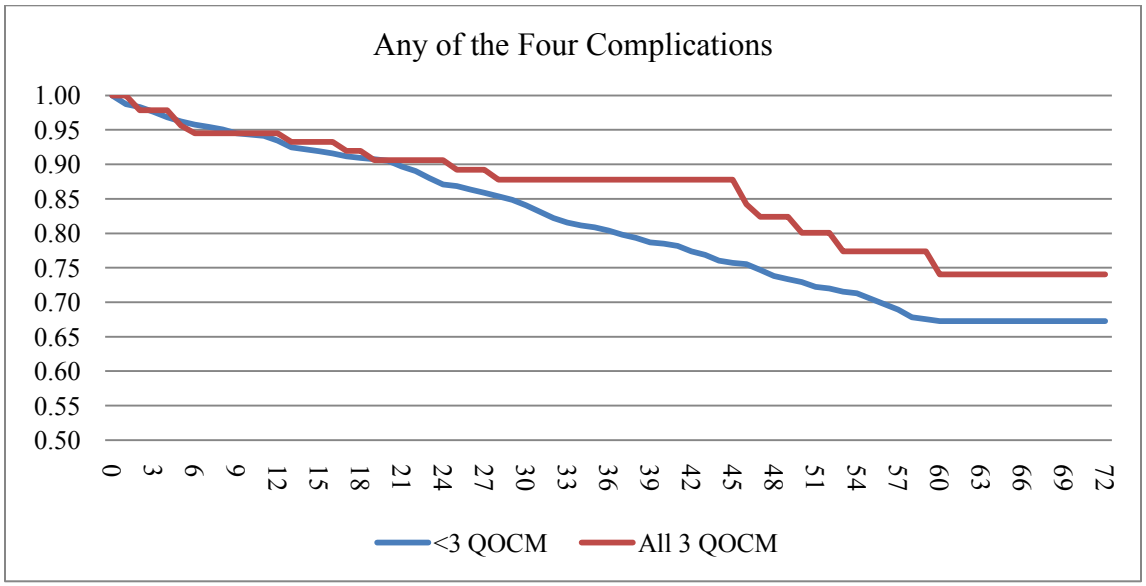
(b) HF (n = 1,765, HR 0.39, 95% CI [0.19 - 0.81], p = 0.0117)



(c) Stroke (n = 1,751, HR 0.63, 95% CI [0.38 – 1.07], p = 0.0891)



(d) RD (n = 1,785, HR 0.48, 95% CI [0.24 – 0.95], p = 0.0339)



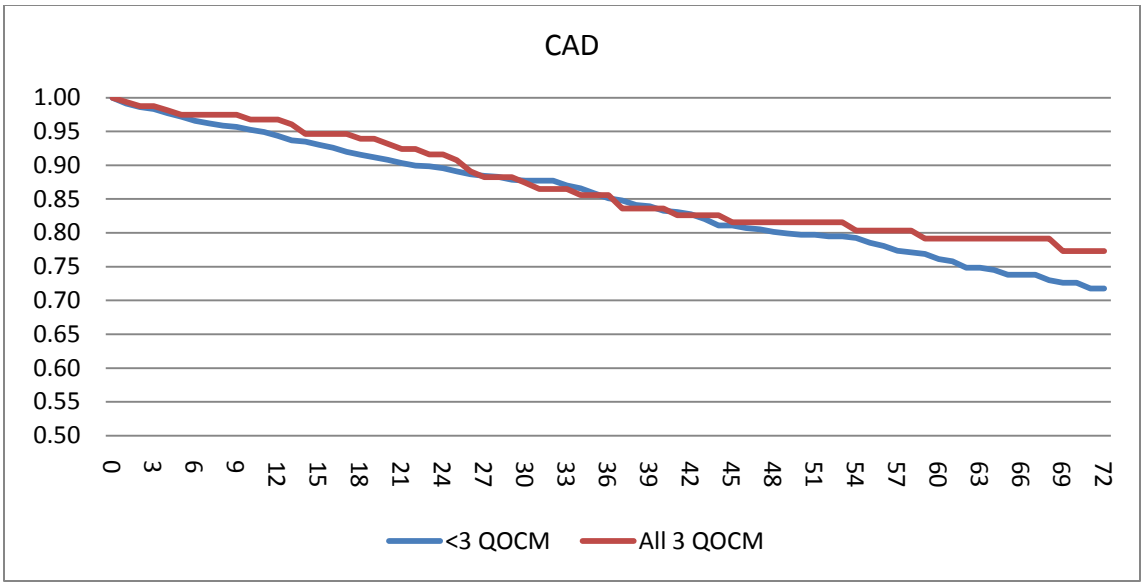
(e) Any of the four complications (n = x, HR 0.66, 95% CI [0.48 – 0.92], p = 0.0101)

Figure 2 (a-e). Kaplan-Meier estimates of cumulative hazard ratios for all complications.

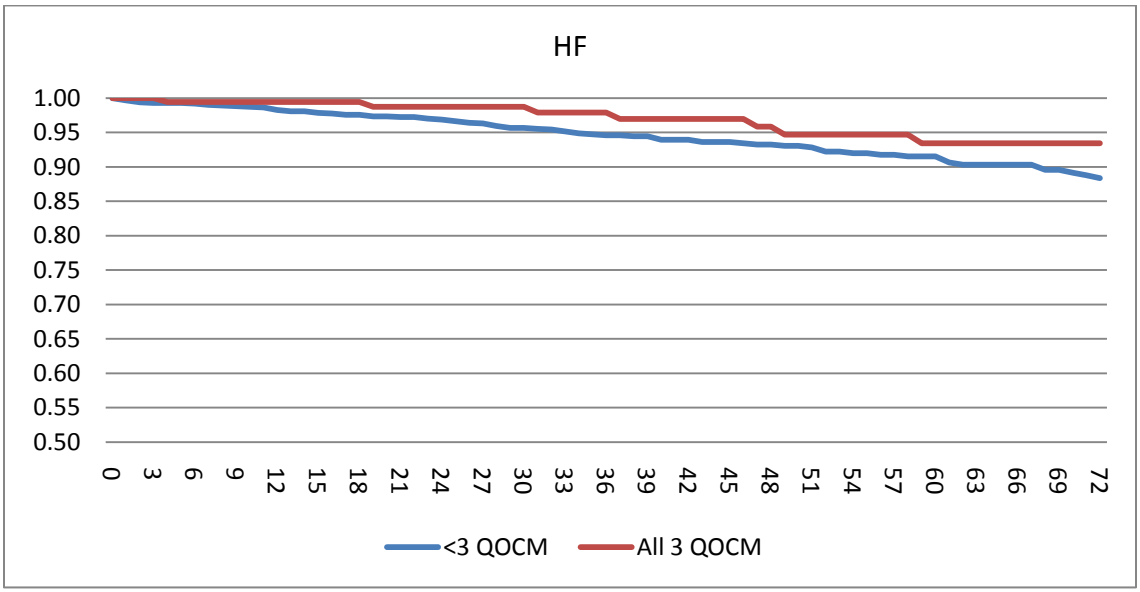
4.6.1 Time trend subgroup analysis for hourly employees

The analysis was repeated after stratifying the data by hourly employee status. The Kaplan-Meier estimates of cumulative hazards for all complications indicate that the differences between the two quality of diabetes care groups began to develop early in the observation period (see Figure 3). The cumulative hazard functions for CAD begin to diverge at six months, converge at 27 months and then diverge again at 42 months, showing benefits through the remainder of the observation period. For HF, the curves separate at nine months and show increasing benefits associated with quality of diabetes care continuing through the end of the observation period. For Stroke, the cumulative hazard functions diverge soon after the end of the baseline period, narrow from 12 to 18 months, and then continue to diverge for the remainder of the six-year observation period. For RD, the cumulative hazard functions diverge at nine months, narrow at 21 months, then diverge until 66 months and converge again for the remainder with the of the observation period. For any of the four complications, the treatment groups begin to diverge at six months with a narrowing at 26 months, and then diverge again at 30 months through the end of the observation period, demonstrating the benefits associated with receiving all three QOCM.

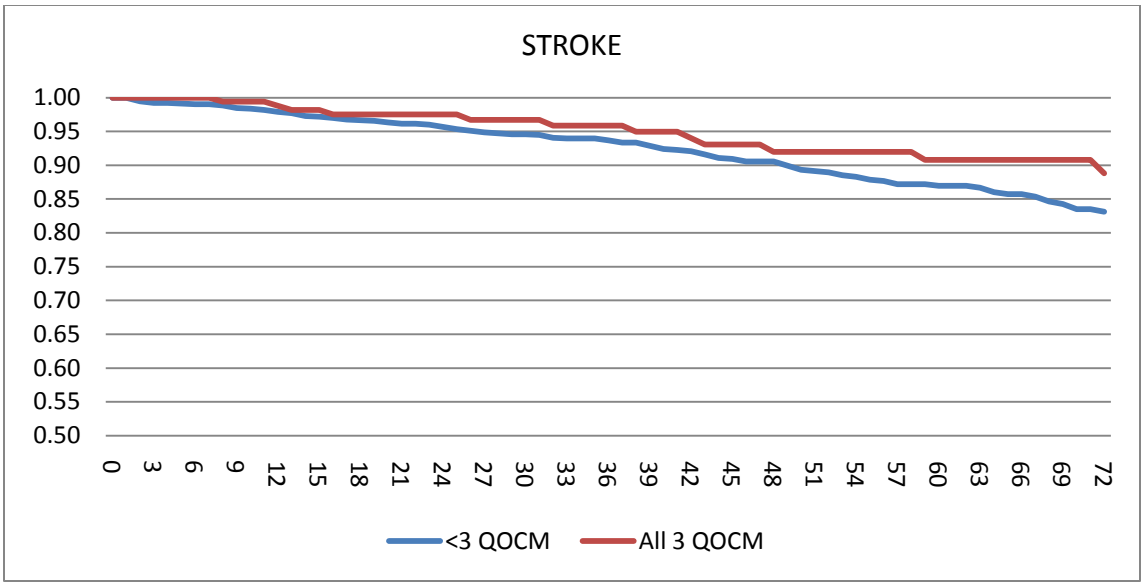
Adjusted models for HF identify that hourly employees who received all three QOCM experienced significantly lower risk for HF (HR 0.432, 95% CI [0.20 - 0.95], p = 0.0374). Based on the adjusted multivariate analysis, hourly employees who received all three QOCM experienced delayed onset of RD (HR 0.42, 95% CI [0.18 - 1.01], p = 0.0527); in fact, hourly employees who received all three QOCM experienced delayed onset for any of the four complications (HR 0.719, 95% CI [0.499 - 1.036], p = 0.0768). Hazard rates for hourly employees are presented in Figure 3 (a-e).



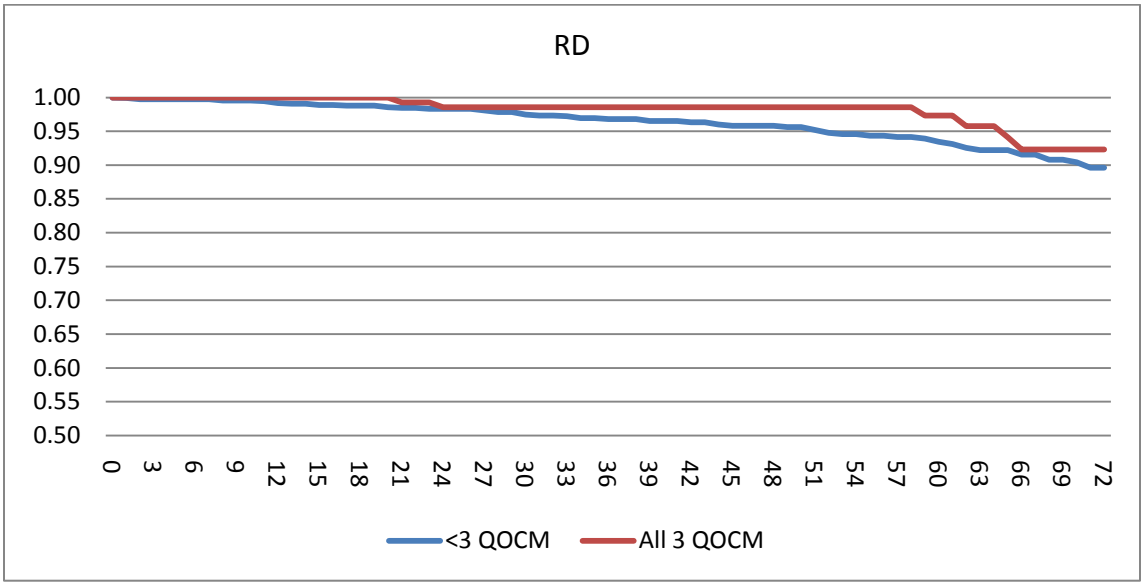
(a) CAD (n = 1,182, HR .075, 95% CI [0.49 - 1.14], p = 0.1751)



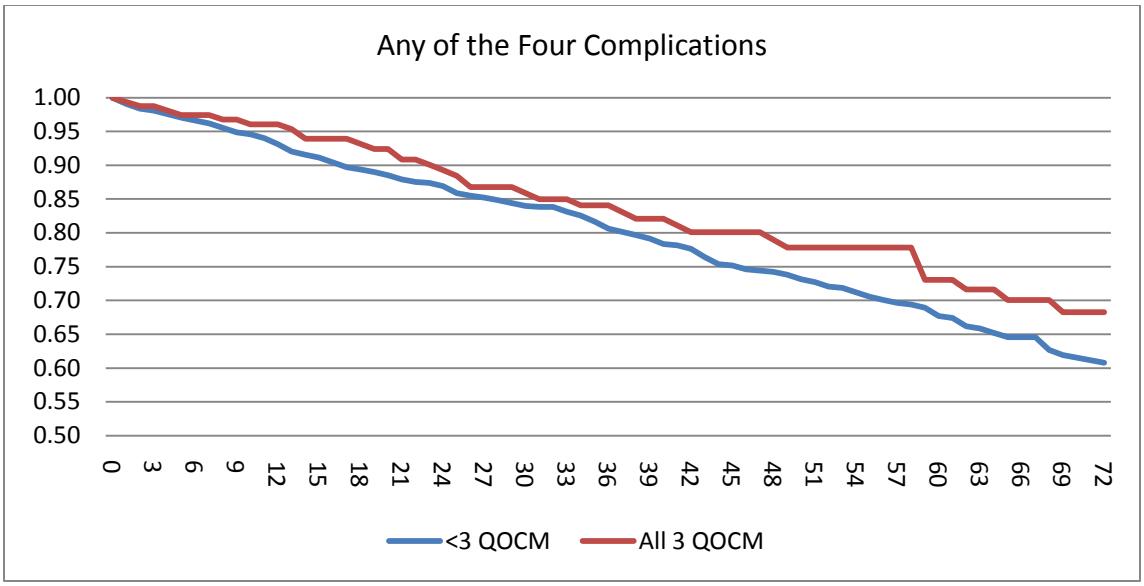
(b) HF (n = 1,335, HR 0.432, 95% CI [0.20 – 0.95], p = 0.0374)



(c) Stroke (n = 1,332, HR 0.68, 95% CI [0.37 – 1.25], p = 0.2116)



(d) RD (n = 1,354, HR 0.42, 95% CI [0.18 = 1.01], p = 0.0527)



(e) Any of the four complications (n = 1,149, HR 0.719, 95% CI [0.499 – 1.036], p = 0.0768)

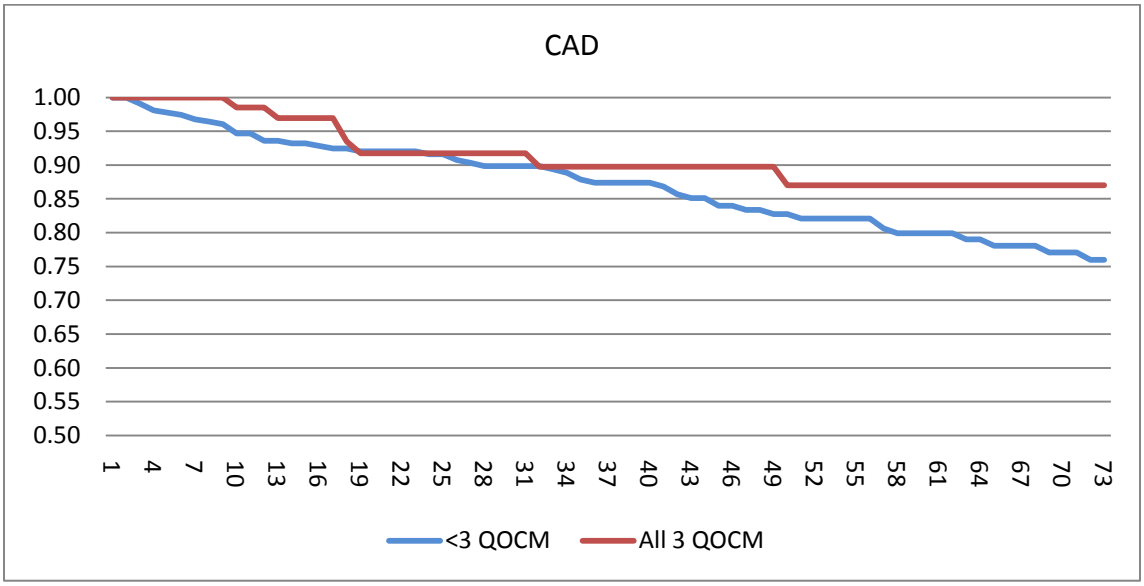
Figure 3 (a-e). Time trend subgroup analysis for hourly employees.

4.6.2 Time trend subgroup analysis for salaried employees

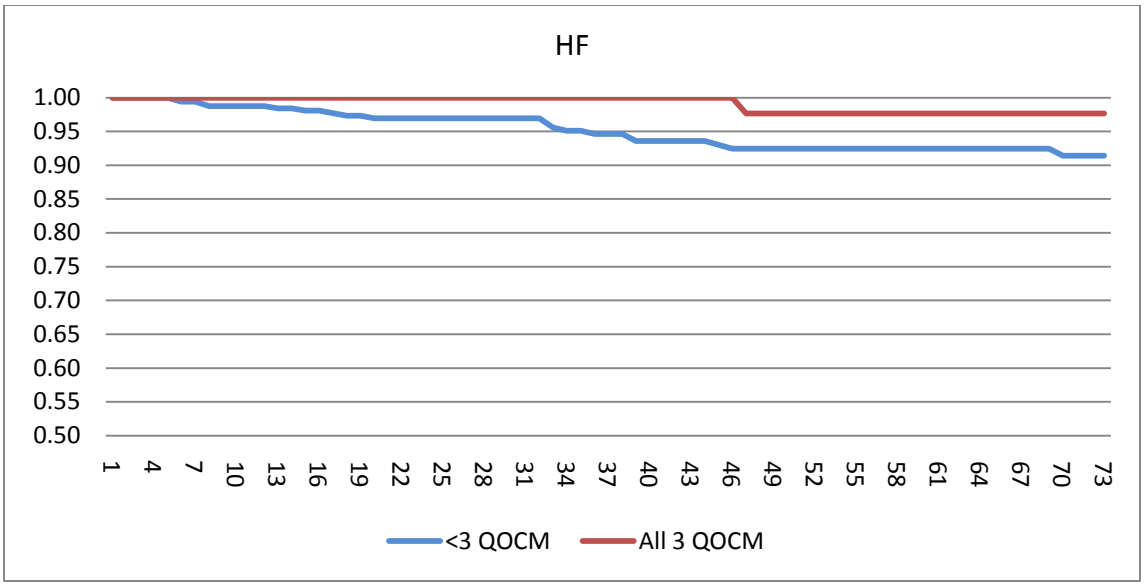
The analysis was repeated after stratifying the data by salaried employee status. The Kaplan-Meier estimates of cumulative hazards for all complications indicate that differences between the two quality of diabetes care groups began to develop early in the observation period (see Figure 4). The cumulative hazard functions for CAD begin to diverge at two months, converge at 19 months and then diverge again at 32 months, showing benefits through the remainder of the observation period. For HF, the curves separate at five months, soon after the baseline period ends, and show increasing benefits associated with quality of diabetes care through the observation period. For Stroke, the cumulative hazard functions diverge at eight months and narrow at 30 months, continuing to demonstrate benefits through the six-year observation period. For renal disease, the cumulative hazard functions are balanced between the two groups, with a

divergence at 64 months. For any of the four complications, the treatment groups begin to diverge at four months and narrow at 27 months. However, the divergence persists through the end of the observation period, demonstrating the benefits associated with receiving all three QOCM.

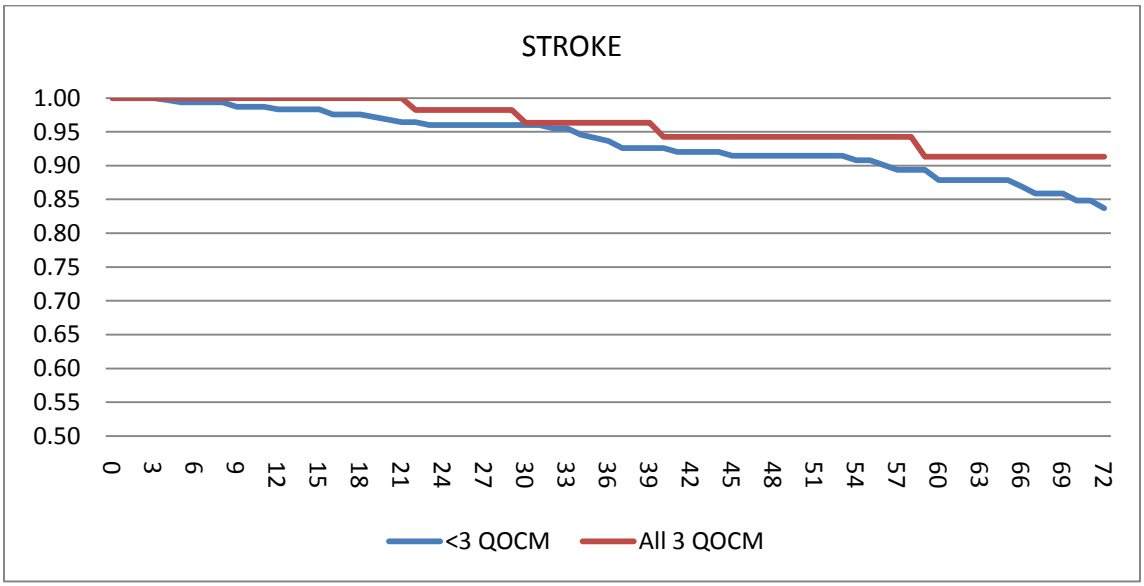
Salaried employees who received all three QOCM in the adjusted multivariate analysis experienced a statistically significant lower risk for developing HF (HR 0.92, 95% CI [0.010 - 0.841], p = 0.0346). Adjusted models show that salaried employees who received all three QOCM also approached a statistically significant delay in the onset of RD (HR 0.27, 95% CI [0.07 - 1.00], p = 0.0501). Similarly, based on the adjusted multivariate analysis, salaried employees who received all three QOCM experienced delayed onset for any of the four complications (HR 0.422, 95% CI [0.216 - 0.846], p = 0.0118). Hazard rates for salaried employees are presented in Figure 4 (a-e).



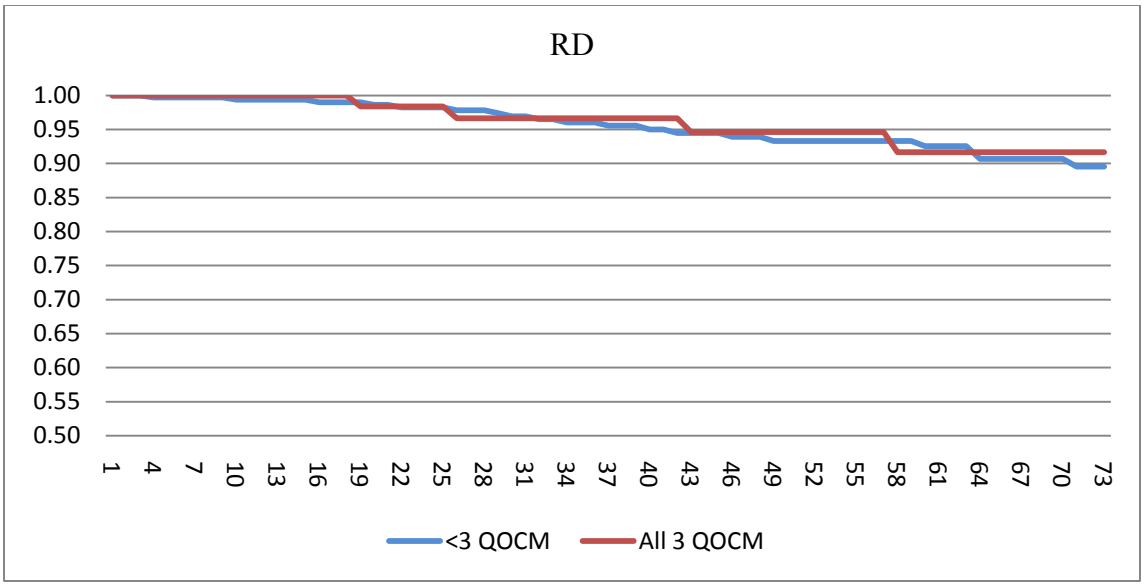
(a) CAD (n = 398, HR 0.48, 95% CI [0.21 – 1.10], p = 0.0841)



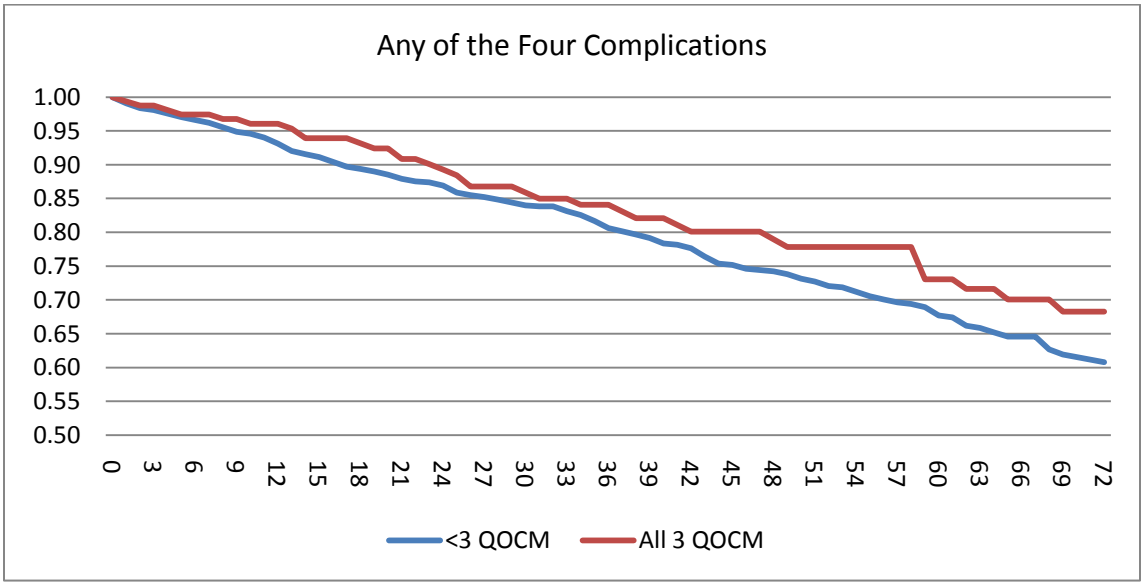
(b) HF (n = 430, HR 0.092, 95% CI [0.010 – 0.841], p = 0.0346)



(c) Stroke (n = 419, HR 0.42, 95% CI [0.14 – 1.30], p = 0.1317)



(d) RD (n = 431, HR 0.27, 95% CI [0.07 – 1.00], p = 0.0501)



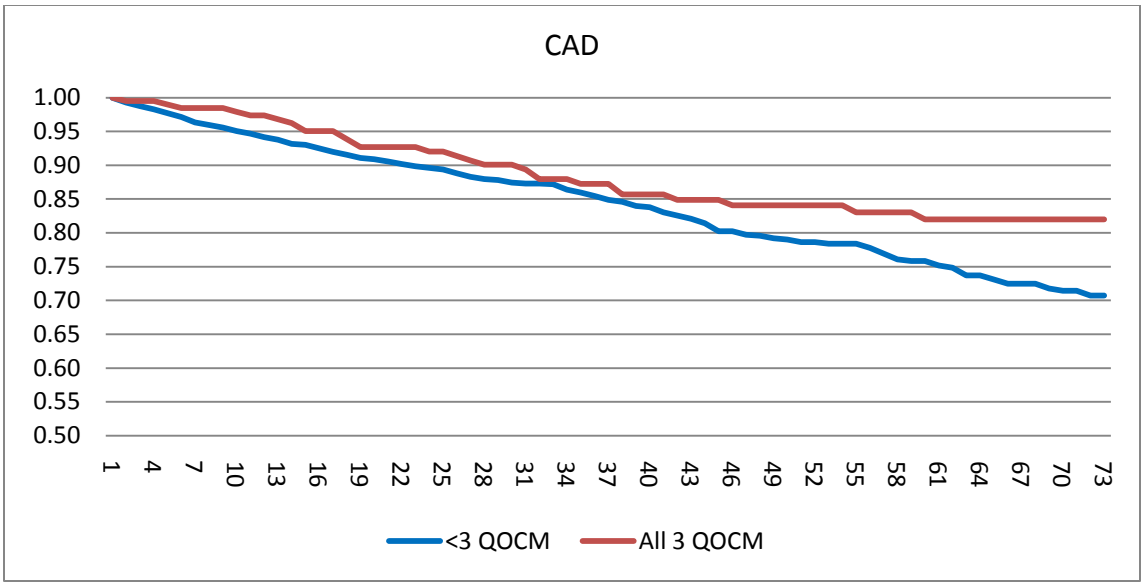
(e) Any of the four complications (n = 377, HR = 0.422, 95% CI [0.216 – 0.826], p = 0.0118)

Figure 4 (a-e). Time trend subgroup analysis for salaried employees.

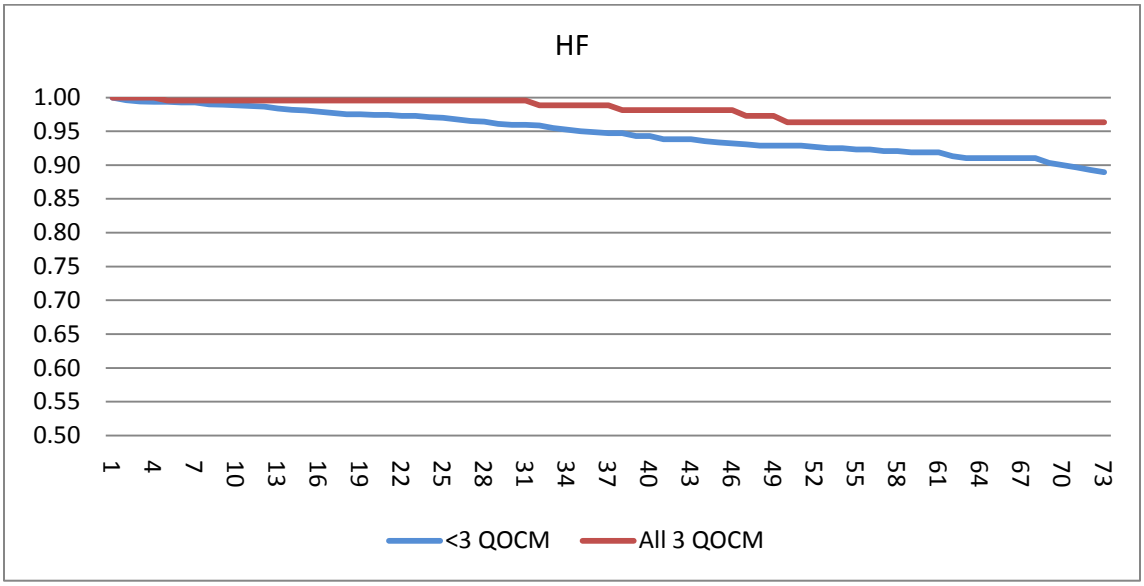
4.6.3 Time trend subgroup analysis for males

The analysis was repeated after stratifying the data by male gender. The Kaplan-Meier cumulative hazard estimates for all complications indicate that differences between the two quality of diabetes care groups began to develop early in the observation period (see Figure 5). The cumulative hazards for CAD begin to diverge at two months, converge at 32 months and then diverge again at 37 months, showing benefits through the remainder of the observation period. For HF, the curves separate at 10 months and show increasing benefits associated with quality of diabetes care continuing through the observation period. For Stroke, the cumulative hazard functions diverge at eight months and continue to demonstrate benefits through the six-year observation period. For RD, the cumulative hazard functions diverge at ten months, narrow at 23 months and then diverge at 28 months for the remainder of the observation period. For any of the four complications, the treatment groups begin to diverge at two months and continue to widen for the remainder of the observation period, demonstrating the benefits associated with receiving all three QOCM.

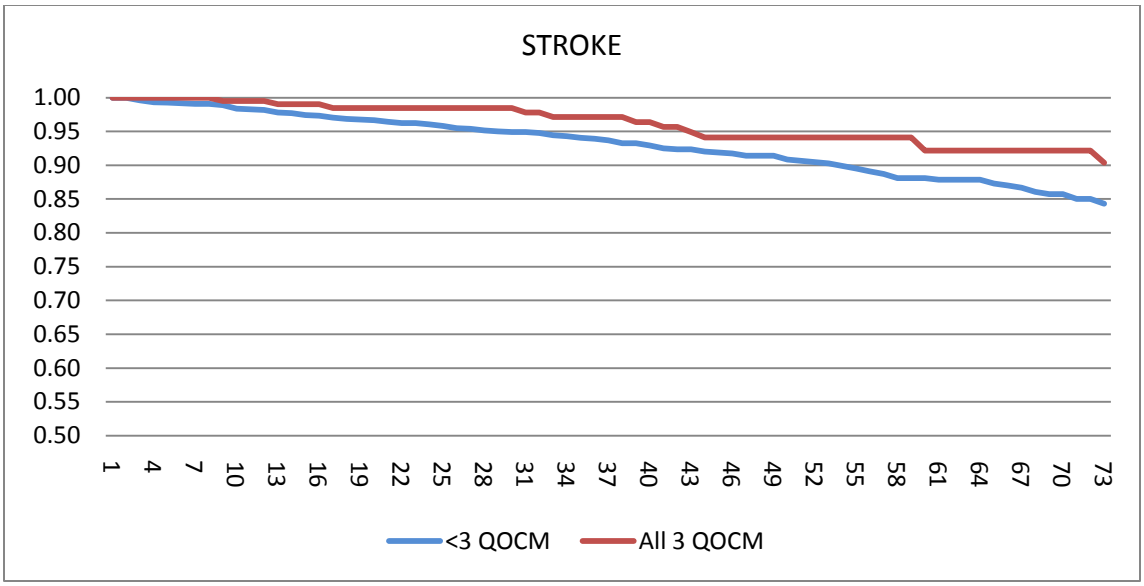
Based on the adjusted multivariate analysis, male diabetics who received all three QOCM experienced lower risk for developing CAD (HR 0.632, 95% CI [0.420 - 0.951], p = 0.0276). Males who received all three QOCM also experienced delayed onset of HF (HR 0.273, 95% CI [0.109 - 0.682], p = 0.0055) and RD (HR 0.371, 95% CI [0.166-0.831], p=0.0160). In fact, the adjusted multivariate analysis indicates that males who received all three QOCM experienced delayed onset for any of the four complications (HR 0.592, 95% CI [0.414 - 0.846], p = 0.0040). Hazard rates for male employees are presented in Figure 5 (a-e).



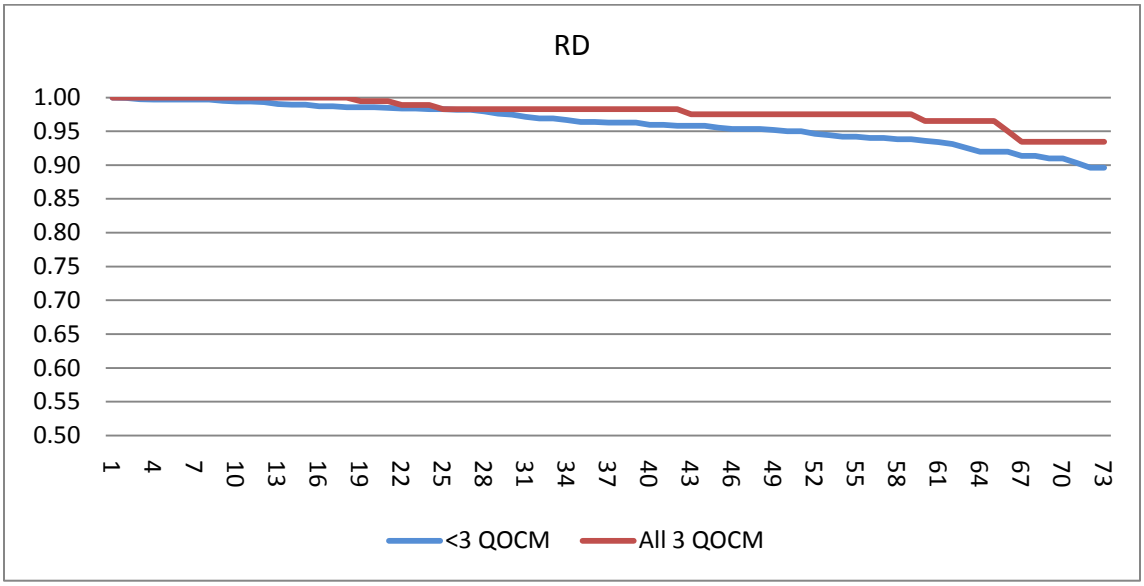
(a) CAD (n = 1,305, HR 0.632, 95% CI [0.420 – 0.951], p = 0.0276)



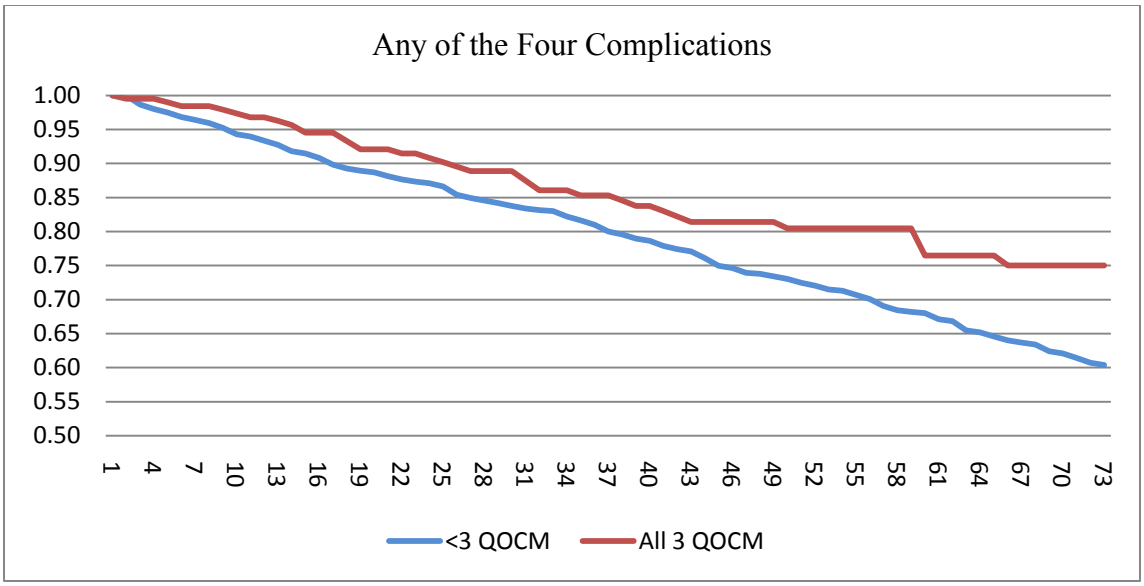
(b) HF (n = 1,467, HR 0.273, 95% CI [1.09 – 0.682], p = 0.0055)



(c) Stroke (n = 1,453, HR 0.581, 95% CI [0.318 – 1.063], p = 0.0781)



(d) RD (n = 1,486, HR 0.371, 95% CI [0.166 – 0.831], p = 0.0160)



(e) Any of the four complications (n = 1,262, HR 0.592, 95% CI [0.414 – 0.846], p = 0.0040)

Figure 5 (a-e). Time trend subgroup analysis for males.

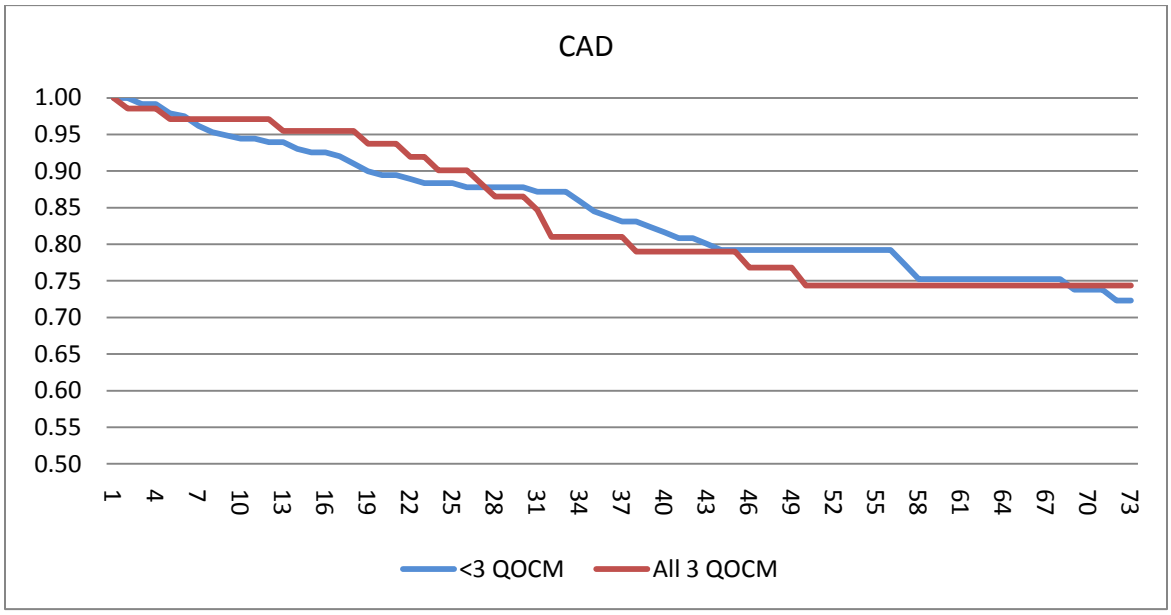
4.6.4 Time trend subgroup analysis for females

The stratum of women shows no evidence of benefit or harm associated with QOCM and CAD, HF, Stroke, RD or for any of the four complications.

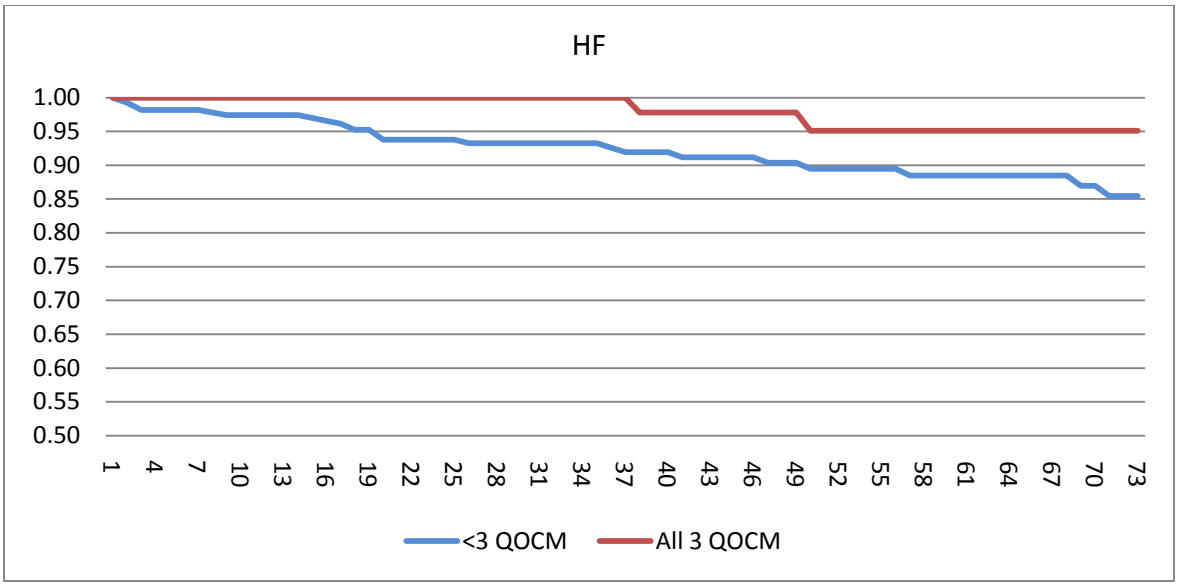
4.6.5 Time trend subgroup analysis for insulin users

The analysis was repeated after stratifying the data based on insulin use. The Kaplan-Meier cumulative hazard estimates for all complications indicate that differences between the two quality of diabetes care groups began to develop early in the observation period (see Figure 6). The cumulative hazard functions for CAD begin to diverge at three months, converge at 32 months and then diverge again at 37 months, showing benefits through the remainder of the observation period. For HF, the curves separate soon after the baseline period ends, at four

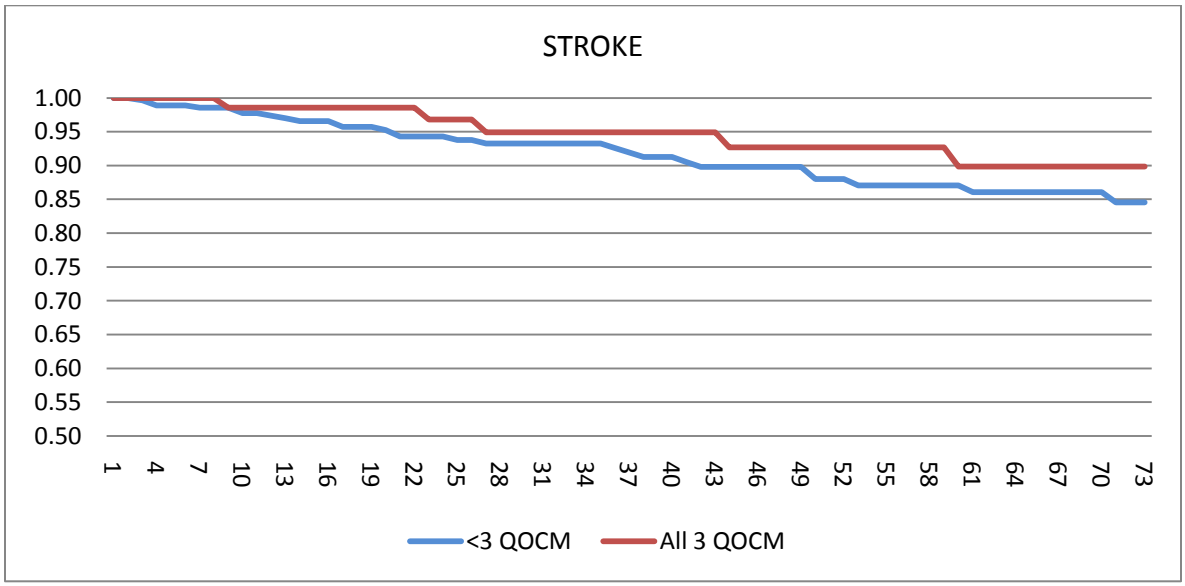
months, and demonstrate increasing benefits associated with higher quality diabetes care continuing through the observation period. For Stroke, the cumulative hazard functions diverge at four months and continue to demonstrate benefits through the six-year observation period. For RD, the cumulative hazard functions diverge at 27 months, narrow at 61 months, and then diverge for the remainder of the observation period. For any of the four complications, the treatment groups begin to diverge at two months with a narrowing at 31 months. However, the divergence persists through the observation period, demonstrating the benefits associated with receiving all three QOCM. Based on the adjusted multivariate analysis, insulin users who received all three QOCM were at lower risk for developing HF (HR 0.190, 95% CI 0.041 – 0.871, p = 0.0325). Hazard rates for insulin users are presented in Figure 6 (a-e).



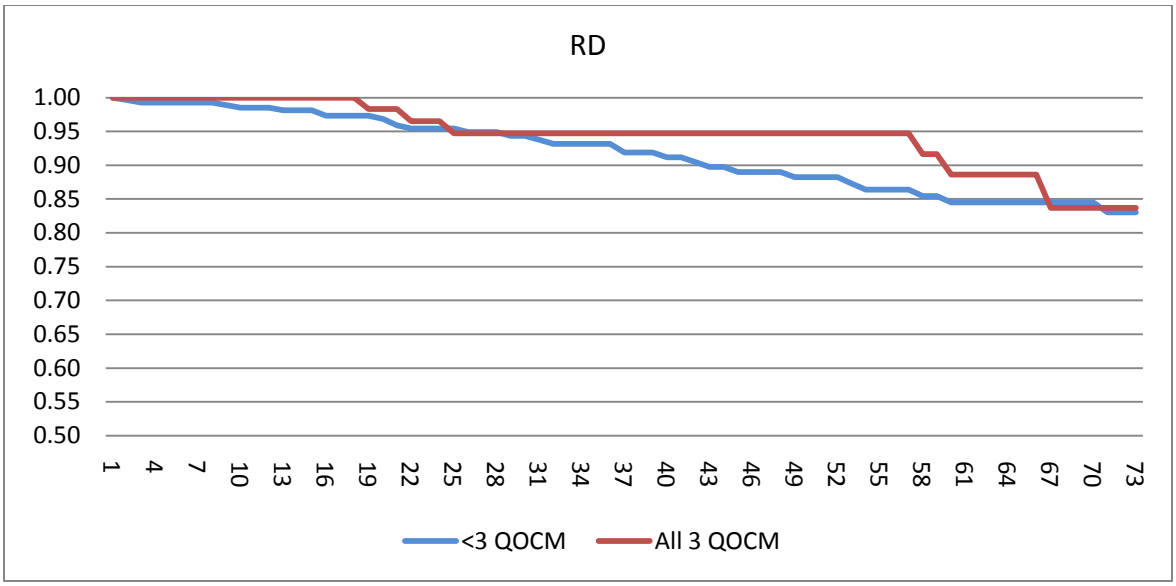
(a) CAD (n = 311, HR 0.898, 95% CI [0.4571 - 1.768], p = 0.7566)



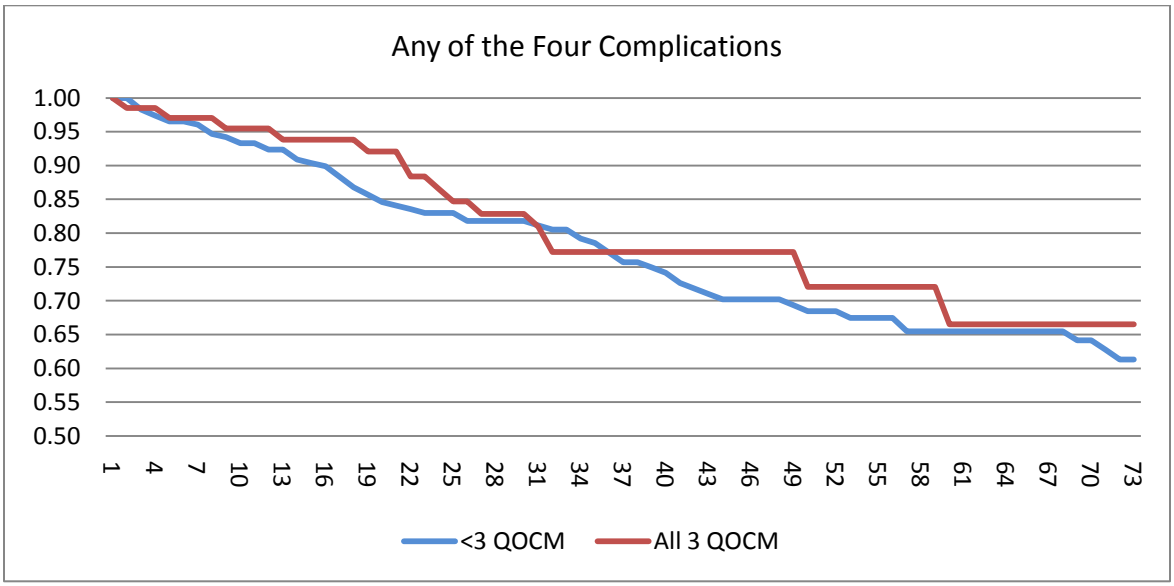
(b) HF (n = 349, HR 0.190, 95% CI [0.041 – 0.871], p = 0.0325)



(c) Stroke (n = 354, HR 0.738, 95% CI [0.264-2.063], p = 0.5619)



(d) RD (n = 357, HR 0.483, 95% CI [0.18 – 1.291], p = 0.1468)



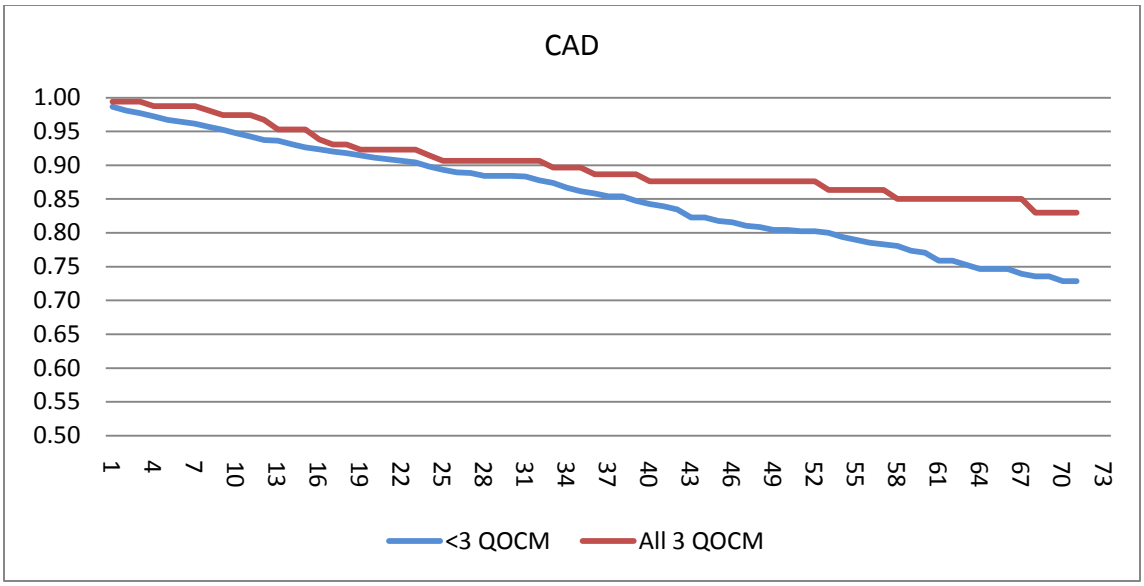
(e) Any of the four complications (n = 300, HR = 0.644, 95% CI [0.349 – 1.186], p = 0.1578)

Figure 6 (a-e). Time trend subgroup analysis for insulin users.

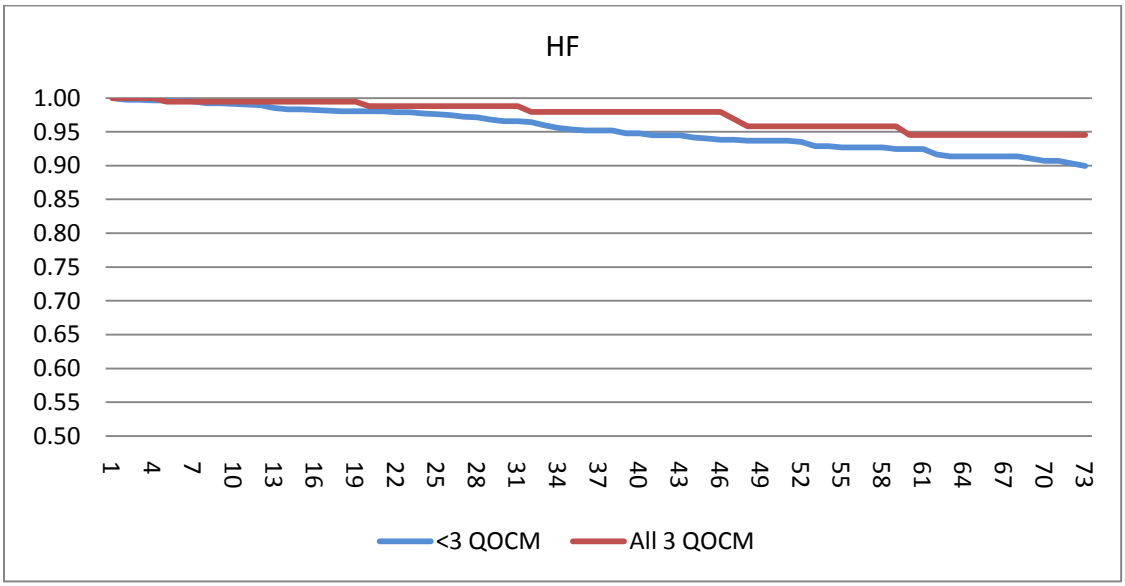
4.6.6 Time trend subgroup analysis for insulin non-users

The analysis was repeated after stratifying the data for insulin non-users. The Kaplan-Meier cumulative hazard estimates for all complications indicate that differences between the two quality of diabetes care groups began to develop early in the observation period (see Figure 7). The cumulative hazards for CAD begin to diverge at three months, converge at 32 months and then diverge again at 37 months, showing benefits through the remainder of the observation period. For HF, the curves separate soon after baseline period at four months, and show increasing benefits associated with quality of diabetes care continuing through the end of the observation period. For Stroke, the cumulative hazard functions diverge at four months and continue to demonstrate benefits through the six-year observation period. For RD, the cumulative hazard functions diverge at 27 months, narrow at 61 months and then diverge for the remainder of the observation period. For any of the four complications, the treatment groups begin to diverge at two months with a narrowing at 31 months.

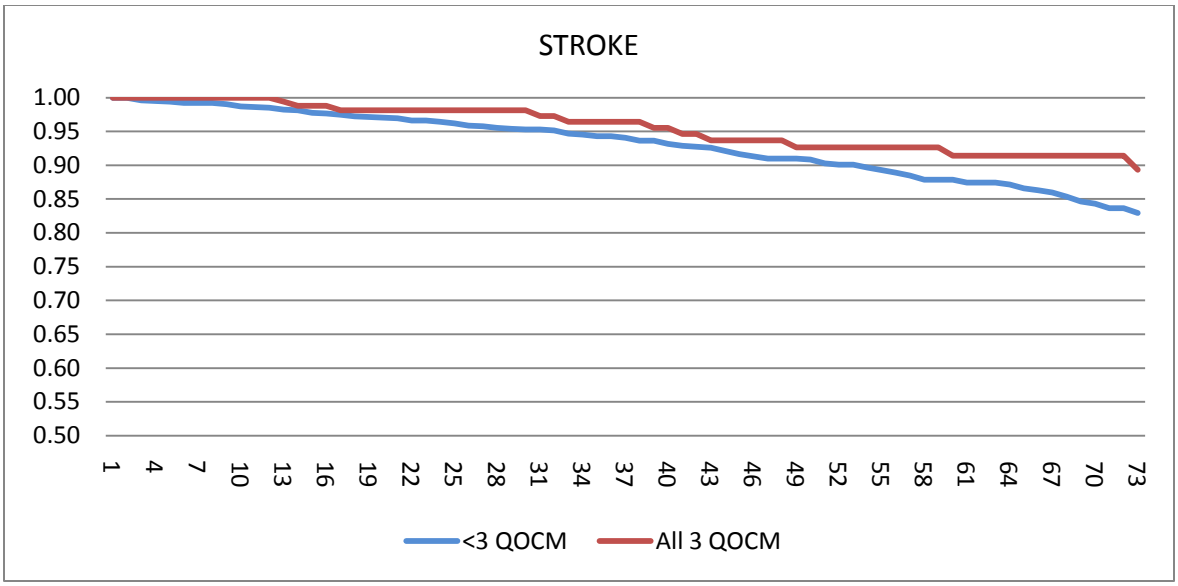
Based on the adjusted multivariate analysis, insulin non-users who received all three QOCM experienced a statistically significant lower risk for developing CAD (HR 0.604, 95% CI [0.375 - 0.972], p = 0.0377). Adjusted models identify that insulin non-users who received all three QOCM also experienced delayed onset of HF (HR 0.445, 95% CI [0.192 - 1.032], p = 0.0593) as well as statistically significant delayed onset for any one of the four complications (HR 0.605, 95% CI [0.408 - 0.896], p = 0.0122). Hazard rates for insulin non-users are presented in Figure 7 (a-e).



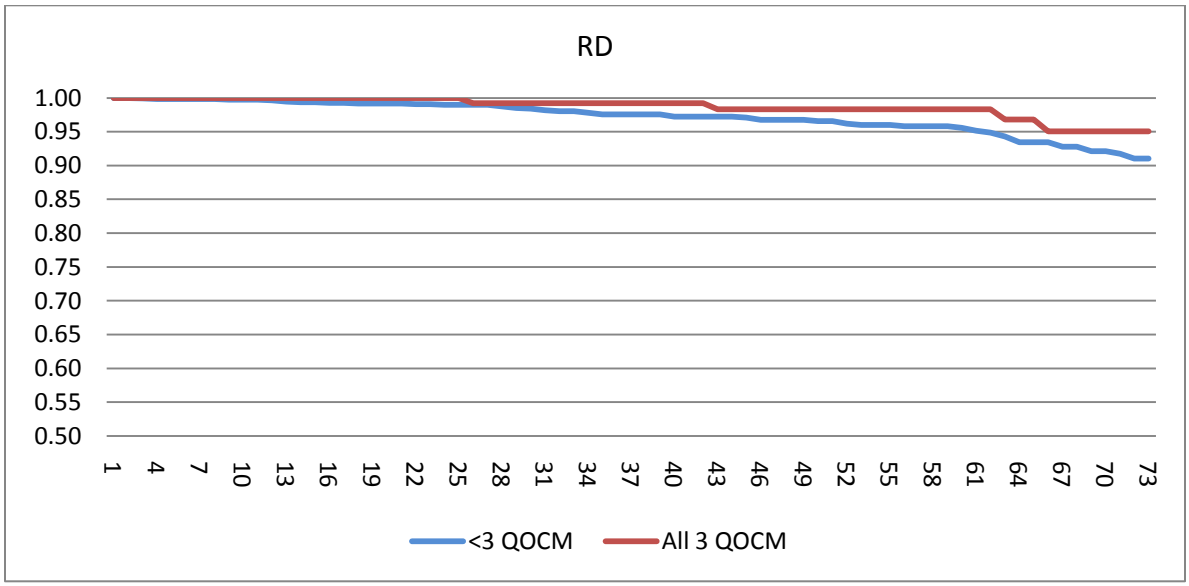
(a) CAD (n = 1,269, HR 0.604, 95% CI [0.375 – 0.972], p = 0.0377)



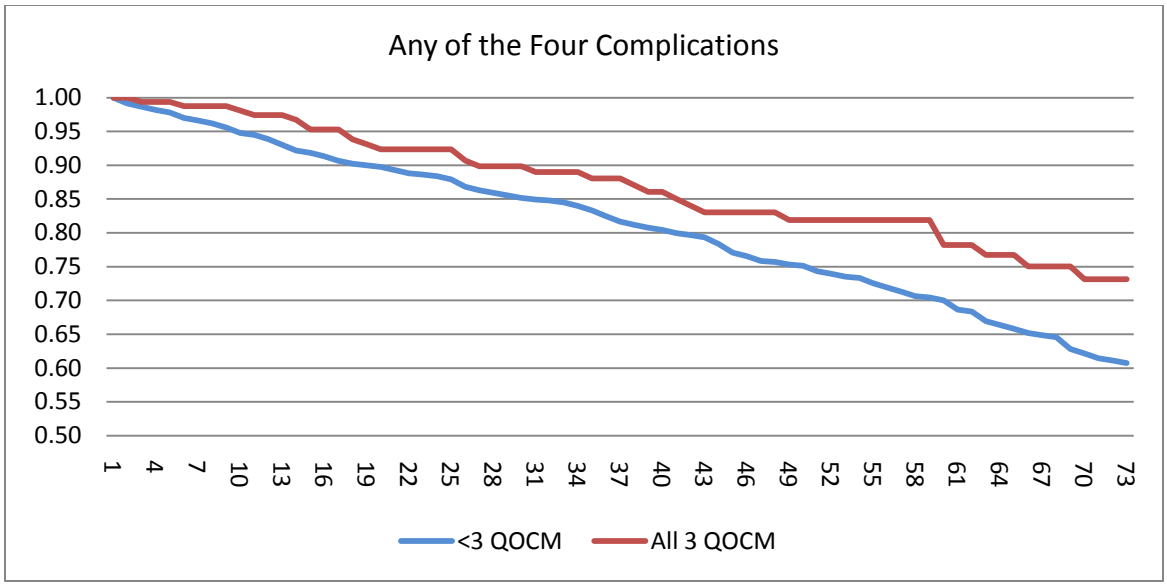
(b) HF (n = 1,416, HR 0.445, 95% CI [0.192 -1.032], p = 0.0593)



(c) Stroke (n = 1,397, HR 0.595, 95% CI [0.319 – 1.111], p = 0.1033)



(d) RD (n = 1,428, HR 0.411, 95% CI [0.147 – 1.148], p = 0.0898)



(e) Any of the four complications (n = 1,226, HR 0.605, 95% CI [0.408 – 0.896], p = 0.0122)

Figure 7 (a-e). Time trend subgroup analyses for non-insulin users.

4.7 SENSITIVITY ANALYSES

The sensitivity analyses based on correlation analysis and Kappa statistics for two years (2003 and 2004) of continuous QOCM were consistent (see Tables 12 and 13). Even though the concordance between the two models as evidenced by the Kappa statistics and correlation analyses are not as strong as anticipated, the trends are the same and the point estimates and 95% CI's are similar. The hazard rates for QOCM in 2003 and 2004 are all in the same direction but not significant (see Table 14). A comparison of these results to those for 2003 only (see Table 11) supports using the signal year of 2003 as the baseline for the analysis.

Table 12. Correlation Coefficients for Number of QOCM

Years	Number of QOCM	Correlation Coefficient
2003 and 2004	4	0.47
2003 and 2004	3	0.44

Table 13. Kappa Statistics for Two Years of Continuous QOCM

QOCM	2003		2004		Received in 2004 (from those who received in 2003)		% Agreement	Kappa*
	n	%	n	%	n	%		
≥ 1 Lipid	985	62.3	1076	68.1	781	79.3	68.4	0.30
≥ 1 A1C	1075	68.0	1148	72.6	924	86.0	76.3	0.43
≥ 2 A1C	693	43.8	711	45.0	458	66.1	69.1	0.37
≥ 1 Microalbuminuria	380	24.0	468	29.6	222	58.4	74.4	0.35
> All 3	236	14.9	300	19	112	47.5	80.2	0.30

* Kappa agreement: < 0 = less than chance; 0 .01 - 0.20 = slight; 0.21 – 0.40 = fair; 0.41 – 0.60 = moderate; 0.61-0.80 = substantial; 0.81 – 0.99 = almost perfect

Table 14. Cox Proportional Hazards Regression Model of the Effect of Receiving all Three QOCM* in 2003 and 2004 on Complications

Complication	Unadjusted HR				Adjusted HR**			
	HR	95% CI		p-value	HR	95% CI		p-value
CAD (n = 1301)	0.71	0.38	1.35	0.30	0.64	0.34	1.23	0.1799
HF (n = 1497)	0.35	0.09	1.44	0.148	0.30	0.07	1.24	0.096
Stroke (n = 1486)	0.56	0.23	1.37	0.201	0.56	0.23	1.38	0.21
RD (n = 1523)	0.77	0.23	2.10	0.603	0.54	0.19	1.53	0.23
Any of the 4 (n = 1285)	0.73	0.44	1.20	0.214	0.65	0.39	1.09	0.104

* 2 A1C measurements, 1 microalbuminuria test, and 1 lipid test in 2003
** Demographics, modifiable risks, clinical measures of risk

5.0 DISCUSSION

This study compared two groups of diabetics to assess how differences in quality of diabetes care affected the onset of four complications associated with diabetes. Significant differences in time-to-complication were observed between the two groups for three of the four complications (CAD, HF and RD) and for any of the four complications when viewed in aggregate. The estimated hazard ratios and 95% confidence intervals for time-to-complication in the models (which were adjusted for demographics, lifestyle factors and health severity risk scores) for those who received all three QOCM were: CAD (HR 0.95, 95% CI [0.91 - 0.98], p = 0.0019), HF (HR 0.39, 95% CI [0.19 - 0.81], p = 0.0117), Stroke (HR 0.95, 95% CI [0.95 – 1.00], p = 0.0382), RD (HR 0.48, 95% CI [0.24 - 0.95], p = 0.0339) and any of the four complications (HR 0.66, 95% CI [0.48 - 0.91], p = 0.0101). There are many studies that assess whether interventions at the provider level improve processes of care and intermediate outcomes, but the effect of such process improvements on complications remains less clear because such outcomes are rarely assessed (Renders et al., 2001). This study estimates the impact of QOCM on reducing the risk of complications by analyzing data across multiple physician groups administering diabetes care within the same health insurance plan structure.

The unadjusted prevalence of diabetes in the study population was 19.7% - more than twice the 8.7% national rate reported by the CDC for adults over the age of 20 (Centers for Disease Control and Prevention, 2003). The case definition in our study may have overestimated

diabetes prevalence since anyone with a prescription for a diabetes drug was classified as a diabetic, even if they were not assigned an ICD-9 code for T1DM or T2DM. In order to classify cases correctly, more accurate coding by physicians is required, particularly in cases where T2DM is treated with insulin, which previously may have been coded as T1DM. In addition, the CDC prevalence rate is based on self-reports, and may underestimate the prevalence of diabetes in the total population.

Despite sample size differences, there were no statistically significant differences between the two study groups at baseline based on demographic, SES or modifiable risk variables, with the exception of insulin prescriptions in the baseline year. On a percentage basis, more diabetics in the group that received all three QOCM used insulin (27.7 %, n = 74) compared to the group that received less than three QOCM (18.8 %, n = 287), which was a statistically significant difference ($p = 0.0007$). Health severity risk scores were also significantly different between the two groups ($p = 0.0429$). Diabetics in the group receiving less than three QOCM were evenly distributed across the quartiles for health severity risk score, whereas those in the group receiving all three QOCM had higher risk scores across Quartiles 2 through 4. In addition to co-morbidities, health severity risk scores include age and gender; as a result, the differences between the two study groups may have been underestimated in the categories of age, gender and insulin use.

In the multivariate analyses (which were adjusted for all covariates), diabetics with increasing health severity risk scores who received all three QOCM experienced lower hazard rates for complications compared to those who received less than three QOCM; this held true across all outcomes and strata. The differences were not necessarily associated with access to care, since all study participants were enrolled in the same health insurance plan; however,

quality of care may have been affected by provider education, provider incentives or patient education.

Certain characteristics were more likely to be associated with developing CAD as a complication of diabetes in the multivariate model (see Table 6). Although males (HR 1.72, 95% CI [1.15 - 2.56], p = 0.008) were significantly more likely to develop CAD than females, the rates among all races did not differ significantly. Increasing age was also associated with increased risk for CAD, especially for those aged 46 to 51 years (HR 1.81, 95% CI [1.24 - 2.54], p=0.002). Smoking, either in the past or during the study, also produced a borderline significant increase in the hazard rate for CAD (HR 1.47, 95% CI [0.97 - 2.21], p = 0.0676). These findings related to increasing age and smoking are consistent with those in national surveillance reports (Cowie et al., 2003) and population-based studies of CAD and diabetes (Rodbard et al., 2007).

As shown in Tables 11 and 12, the sensitivity analyses for two years of continuous optimal care based on correlation analyses and Kappa statistics were consistent. Trends for two years and one year of optimal care (see Table 12) were the same, with similar point estimates and 95% CIs. The hazard rates were all in the same direction, but not significant (see Table 13). Even though the concordance between the two models was not as strong as anticipated, the results supported using the signal year of 2003 as the baseline for the analysis.

5.1 STRENGTHS AND LIMITATIONS

This analysis suggests that quality of diabetes care, as measured by adherence to ADA guidelines for A1C, microalbuminuria and lipid tests, is an independent predictor of diabetes complications - regardless of access to care and other risk factors. Although disease management strategies

have been employed, and improvements in diabetes care have been reported over time in the US (Saaddine et al., 2006; Saaddine et al., 2002), a widely recognized gap still exists between the quality of care diabetics should receive and the care they do receive. Closing this gap remains a major challenge in the United States.

This study has several strengths, including a large sample size of diabetics who were employed by the same US manufacturer and were enrolled in the same health insurance plan. The population was ethnically, socioeconomically and geographically diverse, and processes of diabetes care data were derived from medical insurance claims, versus self-reported surveys. Smoking data were obtained from occupational health medical records, and financial data from company records. Using the health severity risk score allowed for adjustment of comorbidities using data from insured populations, since it could not be assumed that comorbidities would be comparable for the uninsured. Previous studies used the Charlson Index to adjust for comorbidities, but it was not as applicable to this study since it uses Medicare and Medicaid populations to derive comparisons.

A second strength of the study is the statistically significant difference in baseline characteristics for insulin use and health severity risk scores of the study population. At baseline there is evidence of reverse causality. Such disparities should predict more care for those diabetics who are less healthy at baseline – yet, that was not the case. This is further evidence that the study may have underestimated the benefits of good care

A third strength of the study is the setting itself. Random effects are reduced by evaluating the quality of care delivered through the same provider networks within the employment context. This a highly advantageous study setting for analyzing associations of

quality of healthcare and disease outcomes (Einav, Finkelstein, & Cullen, 2010; Einav, Finkelstein, Pascu, & Cullen, Under Review; Einav, Finkelstein, Ryan, Schrimpf, & Cullen).

Another strength of this study, is the use of personnel, financial and administrative health insurance claims data, is also a limitation. Administrative datasets provide verified SES data for sex, age, ethnicity and salary data. The potential for confounding due to misclassification, coding errors and omissions are reduced due to the high quality data for SES measures from the manufacturers personnel and financial records. Additionally, unobserved confounders may affect findings when they are not controlled for adequately in the multivariate analysis. Moreover, rates of adherence to the NCQA HEDIS quality measures may underreport actual quality of care; patients may receive screenings (e.g., dipstick microalbuminuria, finger stick, cholesterol) in a healthcare provider's office or the workplace that are not submitted to the health insurance plan for reimbursement, and thus not included in the administrative claims data.

Another limitation of this study is the inability to fully differentiate between incident and prevalent cases in the baseline year, despite data from the two year pre-study period (2001 and 2002). This was primarily due to the definition of diabetes cases in this study including a combination of office visits, hospitalizations and prescriptions for diabetes medications. This study also demonstrates some of the limitations of using claims datasets. Using claims data to identify diabetes cases as a covariate in statistical models may introduce over and under-ascertainment and possible bias.

The study was also limited by a lack of comparison data in order to assess the effect of QOCM on intermediate outcomes or medication management. Previous reports (Selby et al., 2007) have noted poor concordance between process measures of diabetes care and control of intermediate outcomes, suggesting that disease management programs should focus more

directly on outcomes to improve their control. Successful efforts will likely require a better understanding of the specific patient and provider factors that affect clinical care and patient abilities to manage their diabetes (Selby et al., 2007).

Another limitation is the length of the baseline period. Extending the baseline year from one year to two years would improve case ascertainment; however, it would shorten the observation period and increase the potential for reverse causality (e.g., complications from diabetes leading to more care).

Another important factor is the generalizability of these results. Based on age, sex, tenure and employment status (hourly vs. salary), the 901 employees excluded from the final study were not significantly different from those who were included; therefore, it would seem most likely that the final study population was representative of the total group. Generalizability is limited to the assessed time frame and to insured populations, who may differ from uninsured or publicly-funded patients.[3] Also, due to the gap in the literature related to assessing processes of care and complications of diabetes, these results are not comparable to other studies based on self-reported survey data.

This study only addresses adherence to three NCQA HEDIS measures for diabetes. The analysis does not assess the HEDIS measures associated with foot examinations and dilated retinopathy due to a lack of formal data documenting these procedures. Also, this analysis cannot assert that QOCM are directly related to treatment outcomes. For example, there is no assurance that a specific individual who adheres to the guidelines will achieve goals for intermediate outcomes associated with A1C, lipids or blood pressure. Those with more

[3] It is important to note that since the time of these analyses the US health insurance market has changed, including the elimination of pre-existing conditions as a barrier to insurance and the introduction of free preventive screening for all insured populations.

comorbidities may be more likely to satisfy QOCM requirements, but may still not receive adequate care. During the study period, the health insurance provider did not utilize pay for performance programs with physician providers to improve compliance with NCQA HEDIS measures for diabetes or any other chronic conditions (e.g., asthma, etc.).

Accreditation organizations such as NCQA emphasize simple process of care measures that are easy to document with administrative data (for example, whether A1C was performed). Such approaches focus on intermediate outcome levels and their clinical treatments and ignore adverse outcomes. Thus, health plans and disease management programs developed under accreditation focus more heavily on improving processes than outcomes of care. Our findings support the need for refinements in disease management that shift the focus toward direct measurement and feedback of intermediate outcomes and toward measurement of processes of care that are more directly associated with improved outcomes and reducing complications (Mangione et al., 2006). Improving intermediate outcomes is more challenging than altering care processes, however. Process improvements can be more readily applied to entire populations with diabetes; but, intermediate outcome control requires identifying patients with elevated levels, targeting interventions to their specific needs, and supporting self-management. In addition, control of intermediate outcomes requires the active participation of primary care physicians who may yet lack sufficient knowledge, decision support resources or time to appropriately help patients achieve control (Kerr, Krein, Vijan, Hofer, & Hayward, 2001; Mangione et al., 2006). Future studies should more directly measure which interventions lead to appropriate intensification of treatment and monitoring regimens for intermediate outcomes that are associated with overall risk or risk reduction for specific complications.

Despite these limitations, the study appears to be the first to address the association between NCQA HEDIS measures and diabetes complications in a commercially insured population. While the study is limited by its reliance on administrative claims data, this is the same type of information that health plans are required to use when reporting NCQA measures. Claims data do provide a method for observing real-world treatment patterns that are unavailable in data collected in clinical trials. Thus, this study demonstrates the potential value of using administrative claims data in epidemiologic research on diabetes.

5.2 CONCLUSION

Although there is evidence that disease management for patients with diabetes improves processes of care and glycemic control, there is no evidence that these strategies improve other intermediate outcomes such as blood pressure or lipid control (Kern, 2006; Knight et al., 2005; Norris et al., 2002). This study sought to determine whether adhering to the three QOCM guidelines was associated with reducing the risk of complications associated with diabetes over a six-year observation period. The overall health benefits of diabetics who received all three QOCM at baseline were noteworthy; they experienced reduced risk for HF, RD and any of the four complications compared to the group that received less than three QOCM. The results suggest that receiving all three monitoring tests for diabetes (two A1C tests, one microalbuminuria and one lipid screening per year) is associated with a reduced risk for these complications. Although monitoring intensification can be constrained by patient and provider reluctance (in part because of the associated costs), these results suggest that any improvement in

screening is likely to reduce the risk of diabetes complications, revealing many implications for policy and health plan leaders.

BIBLIOGRAPHY

Abbott, R. D., Donahue, R. P., MacMahon, S. W., Reed, D. M., & Yano, K. (1987). Diabetes and the risk of stroke. *JAMA: The Journal of the American Medical Association, 257*(7), 949.

Abraira, C., Colwell, J., Nuttall, F., Sawin, C. T., Henderson, W., Comstock, J. P., et al. (1997). Cardiovascular events and correlates in the Veterans Affairs Diabetes Feasibility Trial: Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes. *Archives of Internal Medicine, 157*(2), 181-188.

Adler, A. I., Stevens, R. J., Manley, S. E., Bilous, R. W., Cull, C. A., & Holman, R. R. (2003). Development and progression of nephropathy in type 2 diabetes: The United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney International, 63*(1), 225-232.

Adler, A. I., Stratton, I. M., Neil, H. A. W., Yudkin, J. S., Matthews, D. R., Cull, C. A., et al. (2000). Association of systolic blood pressure with macrovascular and microvascular complications of type 2 diabetes (UKPDS 36): Prospective observational study. *British Medical Journal, 321*(7258), 412.

Air, E. L., & Kissela, B. M. (2007). Diabetes, the metabolic syndrome, and ischemic stroke. *Diabetes Care, 30*(12), 3131.

American Diabetes Association. (2005). Standards of Medical Care in Diabetes. *Diabetes Care, 28*, S4.

American Diabetes Association. (2010). Standards of Medical Care in Diabetes - 2010. *Diabetes Care, 34*(3), S11.

Andersson, D. K. G., Lundblad, E., & Svärdsudd, K. (1993). A model for early diagnosis of type 2 diabetes mellitus in primary health care. *Diabetic Medicine, 10*(2), 167-173.

Antonopoulos, S. (2002). Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation, 106*(3143), 3421.

Aronoff, S. L., Berkowitz, K., Shreiner, B., & Want, L. (2004). Glucose metabolism and regulation: Beyond insulin and glucagon. *Diabetes Spectrum, 17*(3), 183.

Bakris, G. L., Williams, M., Dworkin, L., Elliott, W. J., Epstein, M., Toto, R., et al. (2000). Preserving renal function in adults with hypertension and diabetes: A consensus approach. *American Journal of Kidney Diseases, 36*(3), 646-661.

Beckles, G. L., Engelgau, M. M., Narayan, K. M., Herman, W. H., Aubert, R. E., & Williamson, D. F. (1998). Population-based assessment of the level of care among adults with diabetes in the US. *Diabetes Care, 21*(9), 1432.

Bertoni, A. G., Hundley, W. G., Massing, M. W., Bonds, D. E., Burke, G. L., & Goff, D. C. (2004). Heart failure prevalence, incidence, and mortality in the elderly with diabetes. *Diabetes Care, 27*(3), 699-703.

Boudina, S., & Abel, E. D. (2007). Diabetic cardiomyopathy revisited. *Circulation, 115*(25), 3213.

Boyle, J. P., Honeycutt, A. A., Narayan, K. M., Hoerger, T. J., Geiss, L. S., Chen, H., et al. (2001). Projection of diabetes burden through 2050. *Diabetes Care, 24*(11), 1936.

Brown, A. F., Gregg, E. W., Stevens, M. R., Karter, A. J., Weinberger, M., Safford, M. M., et al. (2005). Race, ethnicity, socioeconomic position, and quality of care for adults with diabetes enrolled in managed care. *Diabetes Care, 28*(12), 2864.

Buse, J. B., Rosenstock, J., Sesti, G., Schmidt, W. E., Montanya, E., Brett, J. H., et al. (2009). Liraglutide once a day versus exenatide twice a day for type 2 diabetes: a 26-week randomised, parallel-group, multinational, open-label trial (LEAD-6). *The Lancet, 374*(9683), 39-47.

Calado, J., Loeffler, J., Sakallioglu, O., Gok, F., Lhotta, K., Barata, J., et al. (2006). Familial renal glucosuria: SLC5A2 mutation analysis and evidence of salt-wasting. *Kidney International, 69*(5), 852-855.

Centers for Disease Control and Prevention. (2003). National diabetes fact sheet: United States, 2003. Washington, DC: U.S. Department of Health and Human Services.

Centers for Disease Control and Prevention. (2008). National diabetes fact sheet: General information and national estimates on diabetes in the United States, 2007. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

Centers for Disease Control and Prevention. (2010). National diabetes fact sheet: United States, 2010. Washington, DC: U.S. Department of Health and Human Services.

Centers for Disease Control and Prevention. (2011). National diabetes fact sheet: National estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention.

Chowdhury, P., Balluz, L., Town, M., Chowdhury, F. M., Bartolis, W., Garvin, W., et al. (2010). Surveillance of certain health behaviors and conditions among states and selected local areas - Behavioral Risk Factor Surveillance System, United States, 2007. *CDC MMWR: Morbidity and Mortality Weekly Report, Surveillance Summaries, 59*(1), 1-224.

Clemans-Cope, L., Garrett, B., & Hoffman, C. (2006). *Kaiser Commission on Medicaid and the Uninsured, Changes in employees' health insurance coverage, 2001-2005* Henry J. Kaiser Family Foundation.

Coutinho, M., Gerstein, H. C., Wang, Y., & Yusuf, S. (1999). The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. *Diabetes Care, 22*(2), 233.

Cowie, C. C., Rust, K. F., Byrd-Holt, D., & Eberhardt, M. S. (2003). Prevalence of diabetes and impaired fasting glucose in adults: United States, 1999-2000. *JAMA: The Journal of the American Medical Association, 290*(13), 1702.

Cullen, M. R., Vegso, S., Cantley, L., Galusha, D., Rabinowitz, P., Taiwo, O., et al. (2006). Use of medical insurance claims data for occupational health research. *Journal of Occupational and Environmental Medicine, 48*(10), 1054.

Davis, W. A., Norman, P. E., Bruce, D. G., & Davis, T. M. E. (2006). Predictors, consequences and costs of diabetes-related lower extremity amputation complicating type 2 diabetes: The Fremantle Diabetes Study. *Diabetologia, 49*(11), 2634-2641.

DCCT. (1992). Lipid and lipoprotein levels in patients with insulin-dependent diabetes mellitus (IDDM): Results from the Diabetes Control and Complication Trial (DCCT). *Diabetes Care, 15*(7), 886.

DCCT. (1993). Diabetes Control and Complications Trial and Research Group: The effect of intensive treatment of diabetes on the development and progression of long term complications in insulin dependent diabetes mellitus. *New England Journal of Medicine, 329*(14), 977–986.

DCCT. (1996). Diabetes Control and Complications Trial Research Group: Lifetime benefits and costs of intensive therapy as practiced in the Diabetes Control and Complications Trial. *JAMA: The Journal of the American Medical Association, 276*, 1409-1415.

DCCT/EDIC. (2000). The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group: Nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *New England Journal of Medicine, 342*(6), 381-389.

Duckworth, W., Abraira, C., Moritz, T., Reda, D., Emanuele, N., Reaven, P. D., et al. (2009). Glucose control and vascular complications in veterans with type 2 diabetes. *New England Journal of Medicine, 360*(2), 129-139.

EDIC. (1999). Epidemiology of Diabetes Interventions and Complications Research Group: Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care, 22*, 99-111.

Einav, L., Finkelstein, A., & Cullen, M. R. (2010). Estimating Welfare in Insurance Markets Using Variation in Prices*. *Quarterly Journal of Economics, 125*(3), 877-921.

Einav, L., Finkelstein, A., Pascu, I., & Cullen, M. (Under Review). How general are risk preferences? Choices under uncertainty in different domains.

Einav, L., Finkelstein, A., Ryan, S., Schrimpf, P., & Cullen, M. Selection on moral hazard in health insurance, *NBER Working Paper 16969* (April 2011 ed.).

Engelgau, M. M., Narayan, K. M. V., Thompson, T. J., Boyle, J. P., Williamson, D. F., Manninen, D. L., et al. (1998). The cost-effectiveness of screening for type 2 diabetes. *JAMA: The Journal of the American Medical Association, 280*(20), 1757-1763.

ETDRS. (1991). Early Treatment Diabetic Retinopathy Study Research Group: Early photocoagulation for diabetic retinopathy *Ophthalmology, 98*, 766-785.

Feld, S., Hellman, R., & Dickey, R. A. (2002). The American Association of Clinical Endocrinologists medical guidelines for the management of diabetes mellitus: The AACE system of intensive diabetes self-management--2002 update. *Endocrine Practice, 8*(1), 40-82.

Ferrannini, E. (1998). Insulin resistance versus insulin deficiency in non-insulin-dependent diabetes mellitus: Problems and prospects. *Endocrine Reviews, 19*(4), 477.

Feskens, E. J., & Kromhout, D. (1992). Glucose tolerance and the risk of cardiovascular disease: The Zutphen Study. *Journal of Clinical Epidemiology, 45*, 1327-1334.

Fleming, B. B., Greenfield, S., Engelgau, M. M., Pogach, L. M., Clauser, S. B., & Parrott, M. A. (2001). The diabetes quality improvement project. *Diabetes Care, 24*(10), 1815.

Fong, D. S., Aiello, L., Gardner, T. W., King, G. L., Blankenship, G., Cavallerano, J. D., et al. (2004). Retinopathy in diabetes. *Diabetes Care, 27*(suppl 1), s84.

Fowles, J. B., Rosheim, K., Fowler, E. J., Craft, C., & Arrichiello, L. (1999). The validity of self-reported diabetes quality of care measures. *International Journal for Quality in Health Care, 11*(5), 407.

Fox, C. S., Coady, S., Sorlie, P. D., Levy, D., Meigs, J. B., D'Agostino, R. B., et al. (2004). Trends in cardiovascular complications of diabetes. *JAMA: The Journal of the American Medical Association, 292*(20), 2495.

Fox, C. S., Sullivan, L., D'Agostino, R. B., & Wilson, P. W. F. (2004). The significant effect of diabetes duration on coronary heart disease mortality. *Diabetes Care, 27*(3), 704.

Frank, R. N. (2004). Diabetic retinopathy. *New England Journal of Medicine, 350*, 48-58.

Gæde, P., Vedel, P., Parving, H. H., & Pedersen, O. (1999). Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: The Steno type 2 randomised study. *The Lancet, 353*(9153), 617-622.

Gavin, J. R., Alberti, K., Davidson, M. B., DeFronzo, R. A., Drash, A., Gabbe, S. G., et al. (1997). Report of the expert committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care, 20*(7), 1183-1197.

Genuth, S., Alberti, K. G., Bennett, P., Buse, J., Defronzo, R., Kahn, R., et al. (2003). Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care, 26*(11), 3160.

Gerstein, H. C., Riddle, M. C., Kendall, D. M., Cohen, R. M., Goland, R., Feinglos, M. N., et al. (2007). Glycemia treatment strategies in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *The American Journal of Cardiology, 99*(12), S34-S43.

Gillies, C. L., Lambert, P. C., Abrams, K. R., Sutton, A. J., Cooper, N. J., Hsu, R. T., et al. (2008). Different strategies for screening and prevention of type 2 diabetes in adults: Cost effectiveness analysis. *British Medical Journal, 336*(7654), 1180.

Goldberg, R. B., Mellies, M. J., Sacks, F. M., Moye, L. A., Howard, B. V., Howard, W. J., et al. (1998). Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: Subgroup analyses in the cholesterol and recurrent events (CARE) trial. *Circulation, 98*(23), 2513.

Grant, R. W., Buse, J. B., & Meigs, J. B. (2005). Quality of diabetes care in US academic medical centers. *Diabetes Care, 28*(2), 337.

Gress, T. W., Nieto, F. J., Shahar, E., Wofford, M. R., & Brancati, F. L. (2000). Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus. *New England Journal of Medicine, 342*(13), 905-912.

Gross, J. L., de Azevedo, M. J., Silveiro, S. P., Canani, L. H., Caramori, M. L., & Zelmanovitz, T. (2005). Diabetic nephropathy: Diagnosis, prevention, and treatment. *Diabetes Care, 28*(1), 164.

Grundy, S. M., Benjamin, I. J., Burke, G. L., Chait, A., Eckel, R. H., & Howard, B. V. (1999). Diabetes mellitus: A major risk factor for cardiovascular disease. A joint editorial statement by the American Diabetes Association; the National Heart, Lung, and Blood Institute; the Juvenile Diabetes Foundation International; the National Institute of Diabetes and Digestive and Kidney Diseases; and the American Heart Association. *Circulation, 100*, 1132-1133.

Haffner, S. M., Lehto, S., Rönnemaa, T., Pyörälä, K., & Laakso, M. (1998). Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *New England Journal of Medicine, 339*(4), 229-234.

Harris, M. I., Klein, R., Welborn, T. A., & Knuiman, M. W. (1992). Onset of NIDDM occurs at least 4-7 yr before clinical diagnosis. *Diabetes Care, 15*(7), 815.

Heisler, M., Smith, D. M., Hayward, R. A., Krein, S. L., & Kerr, E. A. (2003). Racial disparities in diabetes care processes, outcomes, and treatment intensity. *Medical Care, 41*(11), 1221.

Herlitz, J., Karlson, B. W., Lindqvist, J., & Sjolin, M. (1998). Rate and mode of death during five years of follow-up among patients with acute chest pain with and without a history of diabetes mellitus. *Diabetic Medicine 15*, 308-314.

Hoffman, C., & Paradise, J. (2008). Health insurance and access to health care in the United States. *Annals of the New York Academy of Sciences, 1136*(1), 149-160.

Holman, R. R., Cull, C. A., Fox, C., & Turner, R. C. (1995). United Kingdom Prospective Diabetes Study (UKPDS) 13: Relative efficacy of randomly allocated diet, sulphonylurea, insulin, or metformin in patients with newly diagnosed non-insulin dependent diabetes followed for three years. *British Medical Journal, 310*(6972), 83–88.

Hu, F. B., Stampfer, M. J., Solomon, C. G., Liu, S., Willett, W. C., Speizer, F. E., et al. (2001). The impact of diabetes mellitus on mortality from all causes and coronary heart disease in women: 20 years of follow-up. *Archives of Internal Medicine, 161*(14), 1717.

Imperatore, G., Cadwell, B. L., Geiss, L., Saadinne, J. B., Williams, D. E., Ford, E. S., et al. (2004). Thirty-year trends in cardiovascular risk factor levels among US adults with diabetes: National Health and Nutrition Examination Surveys, 1971-2000. *American Journal of Epidemiology, 160*(6), 531-539.

Institute of Medicine. (2002). *Care without coverage: Too little, too late*. Washington, DC: National Academies Press.

Institute of Medicine Committee on Health Behavior. (2001). *Research, practice, policy, health and behavior: The interplay of biological, behavioral, and societal influences*: National Academies Press.

Jencks, S. F., Huff, E. D., & Cuerdon, T. (2003). Change in the quality of care delivered to Medicare beneficiaries, 1998-1999 to 2000-2001. *JAMA: The Journal of the American Medical Association, 289*(3), 305.

Kaiser Commission on Medicaid and the Uninsured. (2007). *The uninsured: A primer*. Washington, DC: Henry J. Kaiser Family Foundation.

Kannel, W. B., & McGee, D. L. (1979a). Diabetes and cardiovascular disease. The Framingham Study. *JAMA: The Journal of the American Medical Association, 241*(19), 2035.

Kannel, W. B., & McGee, D. L. (1979b). Diabetes and cardiovascular risk factors: The Framingham Study. *Circulation, 59*(1), 8.

Karter, A. J., Ferrara, A., Liu, J. Y., Moffet, H. H., Ackerson, L. M., & Selby, J. V. (2002). Ethnic disparities in diabetic complications in an insured population. *JAMA: The Journal of the American Medical Association, 287*(19), 2519.

Karter, A. J., Stevens, M. R., Gregg, E. W., Brown, A. F., Tseng, C. W., Marrero, D. G., et al. (2008). Educational disparities in rates of smoking among diabetic adults: The translating research into action for diabetes study. *American Journal of Public Health, 98*(2), 365.

Katon, W. J., Rutter, C., Simon, G., Lin, E. H. B., Ludman, E., Ciechanowski, P., et al. (2005). The association of comorbid depression with mortality in patients with type 2 diabetes. *Diabetes Care, 28*(11), 2668.

Kelly, T. N., Bazzano, L. A., Fonseca, V. A., Thethi, T. K., Reynolds, K., & He, J. (2009). Systematic review: Glucose control and cardiovascular disease in type 2 diabetes. *Annals of Internal Medicine, 151*(6), 394.

Kendall, D. M., Riddle, M. C., Rosenstock, J., Zhuang, D., Kim, D. D., Fineman, M. S., et al. (2005). Effects of exenatide (exendin-4) on glycemic control over 30 weeks in patients with type 2 diabetes treated with metformin and a sulfonylurea. *Diabetes Care, 28*(5), 1083.

Kenny, S. J., Smith, P. J., Goldschmid, M. G., Newman, J. M., & Herman, W. H. (1993). Survey of physician practice behaviors related to diabetes mellitus in the US Physician adherence to consensus recommendations. *Diabetes Care, 16*(11), 1507.

Kern, L. M. (2006). Outcomes research review. *Journal of Clinical Outcomes Management, 13*, 599-600.

Kerr, E. A., Krein, S. L., Vijan, S., Hofer, T. P., & Hayward, R. A. (2001). Avoiding pitfalls in chronic disease quality measurement: a case for the next generation of technical quality measures. *American Journal of Managed Care, 7*(11), 1033-1050.

Khaw, K. T., Wareham, N., Luben, R., Bingham, S., Oakes, S., Welch, A., et al. (2001). Glycated haemoglobin, diabetes, and mortality in men in Norfolk cohort of European Prospective Investigation of Cancer and Nutrition (EPIC-Norfolk). *British Medical Journal, 322*(7277), 15.

Kissela, B. M., Khoury, J., Kleindorfer, D., Woo, D., Schneider, A., Alwell, K., et al. (2005). Epidemiology of ischemic stroke in patients with diabetes. *Diabetes Care, 28*(2), 355.

Klein, R. (1995). Hyperglycemia and microvascular and macrovascular disease in diabetes. *Diabetes Care, 18*(2), 258.

Klein, R., Barrett-Connor, E. L., Blunt, B. A., & Wingard, D. L. (1991). Visual impairment and retinopathy in people with normal glucose tolerance, impaired glucose tolerance, and newly diagnosed NIDDM. *Diabetes Care, 14*(10), 914.

Klein, R., Klein, B. E. K., Moss, S., & DeMets, D. L. (1988). Proteinuria in diabetes. *Archives of Internal Medicine, 148*(1), 181.

Klein, R., Klein, B. E. K., Moss, S. E., Davis, M. D., & DeMets, D. L. (1984). The Wisconsin epidemiologic study of diabetic retinopathy: II. Prevalence and risk of diabetic retinopathy when age at diagnosis is less than 30 years. *Archives of Ophthalmology, 102*(4), 520.

Knight, K., Badamgarav, E., Henning, J. M., Hasselblad, V., Gano Jr, A. D., Ofman, J. J., et al. (2005). A systematic review of diabetes disease management programs. *American Journal of Managed Care, 11*(4), 242-250.

Knowler, W. C., Barrett-Connor, E., Fowler, S. E., Hamman, R. F., Lachin, J. M., Walker, E. A., et al. (2002). Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *The New England Journal of Medicine, 346*(6), 393.

Koro, C. E., Bowlin, S. J., Bourgeois, N., & Fedder, D. O. (2004). Glycemic control from 1988 to 2000 among US adults diagnosed with type 2 diabetes. *Diabetes Care, 27*(1), 17.

Krolewski, A. S., Kosinski, E. J., Warram, J. H., Stevens Leland, O., Busick, E. J., Cader Asmal, A., et al. (1987). Magnitude and determinants of coronary artery disease in juvenile-onset, insulin-dependent diabetes mellitus* 1. *The American Journal of Cardiology, 59*(8), 750-755.

Kuller, L. H. (1995). *National Diabetes Data Group. Stroke and diabetes*. Bethesda, MD: National Institutes of Health/National Institute of Diabetes/Digestive and Kidney Diseases.

Kuusisto, J., Mykkanen, L., Pyorala, K., & Laakso, M. (1994). Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke, 25*, 1157-1164.

Lanting, L. C., Joung, I., Mackenbach, J. P., Lamberts, S. W. J., & Bootsma, A. H. (2005). Ethnic differences in mortality, end-stage complications, and quality of care among diabetic patients. *Diabetes Care, 28*(9), 2280.

Levin, A., & Rocco, M. (2007). Clinical practice guidelines and clinical practice recommendations for diabetes and chronic kidney disease. *American Journal of Kidney Diseases, 49*(2 Suppl 2), S13-19.

Lewis, E. J., Hunsicker, L. G., Clarke, W. R., Berl, T., Pohl, M. A., Lewis, J. B., et al. (2001). Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *New England Journal of Medicine, 345*(12), 851-860.

Libby, P., Nathan, D. M., Abraham, K., Brunzell, J. D., Fradkin, J. E., Haffner, S. M., et al. (2005). Report of the National Heart, Lung, and Blood Institute-National Institute of Diabetes and Digestive and Kidney Diseases working group on cardiovascular complications of type 1 diabetes mellitus. *Circulation, 111*(25), 3489.

Lillioja, S., Mott, D. M., Spraul, M., Ferraro, R., Foley, J. E., Ravussin, E., et al. (1993). Insulin resistance and insulin secretory dysfunction as precursors of non-insulin-dependent diabetes mellitus: Prospective studies of Pima Indians. *New England Journal of Medicine, 329*(27), 1988-1992.

Litzelman, D. K., Slemenda, C. W., Langefeld, C. D., Hays, L. M., Welch, M. A., Bild, D. E., et al. (1993). Reduction of lower extremity clinical abnormalities in patients with non-insulin-dependent diabetes mellitus. *Annals of Internal Medicine, 119*(1), 36.

Mangione, C. M., Gerzoff, R. B., Williamson, D. F., Steers, W. N., Kerr, E. A., Brown, A. F., et al. (2006). The association between quality of care and the intensity of diabetes disease management programs. *Annals of Internal Medicine, 145*(2), 107.

Mann, J. F. E. (2000). Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: Results of the HOPE study and MICRO-HOPE substudy. *Lancet, 355*(9200), 253-259.

Margetts, B. M. (1995). United Kingdom Prospective Diabetes Study: Compliance with diet will affect results. *British Medical Journal, 310*(6985), 1005.

Martin, T. L., Selby, J. V., & Zhang, D. (1995). Physician and patient prevention practices in NIDDM in a large urban managed-care organization. *Diabetes Care, 18*(8), 1124.

McClain, M. R., Wennberg, D. E., Sherwin, R. W., Steinmann, W. C., & Rice, J. C. (2003). Trends in the diabetes quality improvement project measures in Maine from 1994 to 1999. *Diabetes Care, 26*(3), 597.

McGinnis, J. M., Williams-Russo, P., & Knickman, J. R. (2002). The case for more active policy attention to health promotion. *Health Affairs, 21*(2), 78.

Miettinen, H., Lehto, S., Salomaa, V., Mähönen, M., Niemelä, M., Haffner, S. M., et al. (1998). Impact of diabetes on mortality after the first myocardial infarction. The FINMONICA Myocardial Infarction Register Study Group. *Diabetes Care, 21*(1), 69.

Mohamed, Q., Gillies, M. C., & Wong, T. Y. (2007). Management of diabetic retinopathy: A systematic review. *JAMA: The Journal of the American Medical Association, 298*(8), 902-916.

Narayan, K. M., Boyle, J. P., Thompson, T. J., Sorensen, S. W., & Williamson, D. F. (2003). Lifetime risk for diabetes mellitus in the United States. *JAMA: The Journal of the American Medical Association, 290*(14), 1884.

Nathan, D. M. (2009). International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. *Diabetes Care, 32*(12), e160.

Nathan, D. M., Cleary, P. A., Backlund, J. Y., Genuth, S. M., Lachin, J. M., Orchard, T. J., et al. (2005). 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. *New England Journal of Medicine, 353*(25), 2643-2653.

Nathan, D. M., Zinman, B., Cleary, P. A., Backlund, J. Y., Genuth, S., Miller, R., et al. (2009). Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications and Pittsburgh Epidemiology of Diabetes Complications experience (1983–2005). *Archives of Internal Medicine, 169*, 1307-1316.

Newman, D. J., Mattock, M. B., Dawnay, A. B., Kerry, S., McGuire, A., Yaqoob, M., et al. (2005). Systematic review on urine albumin testing for early detection of diabetic complications. *Health Technology Assessment, 9*(30), 85-115.

Nichols, G. A., Gullion, C. M., Koro, C. E., Ephross, S. A., & Brown, J. B. (2004). The incidence of congestive heart failure in type 2 diabetes. *Diabetes Care, 27*(8), 1879.

Nichols, G. A., Hillier, T. A., Erbey, J. R., & Brown, J. B. (2001). Congestive heart failure in type 2 diabetes: Prevalence, incidence and risk factors. *Diabetes Care, 24*(9), 1614.

Norris, S. L., Nichols, P. J., Caspersen, C. J., Glasgow, R. E., Engelgau, M. M., & Jack, L. (2002). The effectiveness of disease and case management for people with diabetes: A systematic review. *American Journal of Preventive Medicine, 22*(4), 15-38.

O'Brien, T., Nguyen, T. T., & Zimmerman, B. R. (1998). Hyperlipidemia and diabetes mellitus. *Mayo Clinic Proceedings, 73*(10), 969.

Ohkubo, Y., Kishikawa, H., Araki, E., Miyata, T., Isami, S., Motoyoshi, S., et al. (1995). Intensive insulin therapy prevents the progression of microvascular complications in Japanese patients with non-insulin dependent diabetes mellitus: A randomized prospective 6-year study. *Diabetes Research and Clinical Practice, 28*, 103-117.

Parfrey, P. S. (2009). Angiotensin-receptor blockers in the prevention or treatment of microalbuminuria. *Annals of Internal Medicine, 151*(1), 63.

Parving, H. H., Hommel, E., Mathiesen, E., Skøtt, P., Edsberg, B., Bahnsen, M., et al. (1988). Prevalence of microalbuminuria, arterial hypertension, retinopathy, and neuropathy in patients with insulin dependent diabetes. *British Medical Journal (Clinical Research Edition), 296*(6616), 156.

Perneger, T. V., Brancati, F. L., Whelton, P. K., & Klag, M. J. (1994). End-stage renal disease attributable to diabetes mellitus. *Annals of Internal Medicine, 121*(12), 912.

Petersen, M. (2008). Economic costs of diabetes in the US in 2007. *Diabetes Care, 31*(3), 596–615.

Phillips, C. A., & Molitch, M. E. (1995). The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the Diabetes Control and Complications Trial. *Diabetes, 44*, 968-983.

Pitale, S. U., Abraira, C., Emanuele, N. V., McCarren, M., Henderson, W. G., Pacold, I., et al. (2000). Two years of intensive glycemic control and left ventricular function in the Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus (VA CSDM). *Diabetes Care, 23*(9), 1316.

Ray, K. K., Seshasai, S. R. K., Wijesuriya, S., Sivakumaran, R., Nethercott, S., Preiss, D., et al. (2009). Effect of intensive control of glucose on cardiovascular outcomes and death in patients with diabetes mellitus: a meta-analysis of randomised controlled trials. *The Lancet, 373*(9677), 1765-1772.

Renders, C. M., Valk, G. D., Griffin, S. J., Wagner, E. H., Eijk Van, J. T., & Assendelfi, W. J. J. (2001). Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. *Diabetes Care, 24*(10), 1821-1833.

Rodbard, H. W., Blonde, L., Braithwaite, S. S., Brett, E. M., Cobin, R. H., Handelsman, Y., et al. (2007). American Association of Clinical Endocrinologists medical guidelines for clinical practice for the management of diabetes mellitus. *Endocrine Practice, 13*, 1-68.

Roubideaux, Y., Buchwald, D., Beals, J., Middlebrook, D., Manson, S., Muneta, B., et al. (2004). Measuring the quality of diabetes care for older American Indians and Alaska natives. *American Journal of Public Health, 94*(1), 60.

Saaddine, J. B., Cadwell, B., Gregg, E. W., Engelgau, M. M., Vinicor, F., Imperatore, G., et al. (2006). Improvements in diabetes processes of care and intermediate outcomes: United States, 1988–2002. *Annals of Internal Medicine, 144*(7), 465.

Saaddine, J. B., Engelgau, M. M., Beckles, G. L., Gregg, E. W., Thompson, T. J., & Narayan, K. M. (2002). A diabetes report card for the United States: Quality of care in the 1990s. *Annals of Internal Medicine, 136*(8), 565.

Samsom, M., Szarka, L. A., Camilleri, M., Vella, A., Zinsmeister, A. R., & Rizza, R. A. (2000). Pramlintide, an amylin analog, selectively delays gastric emptying: potential role of vagal inhibition. *American Journal of Physiology-Gastrointestinal and Liver Physiology, 278*(6), G946.

Sawin, C. T., Walder, D. J., Bross, D. S., & Pogach, L. M. (2004). Diabetes process and outcome measures in the Department of Veterans Affairs. *Diabetes Care, 27*(Supplement 2), B90.

Saydah, S. H., Fradkin, J., & Cowie, C. C. (2004). Poor control of risk factors for vascular disease among adults with previously diagnosed diabetes. *JAMA: The Journal of the American Medical Association, 291*(3), 335.

Selby, J. V., Swain, B. E., Gerzoff, R. B., Karter, A. J., Waitzfelder, B. E., Brown, A. F., et al. (2007). Understanding the gap between good processes of diabetes care and poor intermediate outcomes: Translating Research into Action for Diabetes (TRIAD). *Medical Care, 45*(12), 1144.

Selvin, E., Marinopoulos, S., Berkenblit, G., Rami, T., Brancati, F. L., Powe, N. R., et al. (2004). Meta-analysis: Glycosylated hemoglobin and cardiovascular disease in diabetes mellitus. *Annals of Internal Medicine, 141*(6), 421.

Singh, N., Armstrong, D. G., & Lipsky, B. A. (2005). Preventing foot ulcers in patients with diabetes. *JAMA: The Journal of the American Medical Association, 293*(2), 217.

Smedley, B. D., Stith, A. Y., & Nelson, A. R. (2002). *Institute of Medicine Committee on Understanding and Eliminating Racial and Ethnic Disparities in Health Care. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care*. Washington, DC: National Academies Press.

Sowers, J. R. (2003). Recommendations for special populations: diabetes mellitus and the metabolic syndrome. *American Journal of Hypertension, 16*(11), 41-45.

Sowers, J. R., & Epstein, M. (1995). Diabetes mellitus and associated hypertension, vascular disease, and nephropathy: An update. *Hypertension, 26*(6), 869.

Sowers, J. R., Epstein, M., & Frohlich, E. D. (2001). Diabetes, hypertension, and cardiovascular disease: An update. *Hypertension, 37*(4), 1053.

Stamler, J., Vaccaro, O., Neaton, J. D., & Wentworth, D. (1993). Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care, 16*(2), 434.

Stratton, I. M., Adler, A. I., Neil, H. A., Matthews, D. R., Manley, S. E., Cull, C. A., et al. (2003). American Diabetes Association: standards of medical care for patients with diabetes mellitus. *Diabetes Care, 26*(Suppl 1), S33-S50.

Stratton, I. M., Adler, A. I., Neil, H. A. W., Matthews, D. R., Manley, S. E., Cull, C. A., et al. (2000). Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): Prospective observational study. *British Medical Journal, 321*(7258), 405.

Strippoli, G. F. M., Craig, M., Schena, F. P., & Craig, J. C. (2005). Antihypertensive agents for primary prevention of diabetic nephropathy. *Journal of the American Society of Nephrology, 16*(10), 3081.

Tunceli, K., Bradley, C. J., Nerenz, D., Williams, L., Pladevall, M., & Elston Lafata, J. (2005). The impact of diabetes on employment and work productivity. *Diabetes Care, 28*(11), 2662.

Tuomilehto, J. (2003). Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? *Diabetes Care, 26*, 688-696.

Turner, R. C., Cull, C. A., Stratton, I. M., Manley, S. E., Kohner, E. M., & Matthews, D. R. (1995). United Kingdom Prospective Diabetes Study 16. Overview of 6 years' therapy of type II diabetes: A progressive disease *Diabetes, 44*, 1249-1258.

Turner, R. C., Stratton, I., Fright, V., Holman, R., Manley, S., & Cull, C. (1993). Hypertension in Diabetes Study (HDS): I. Prevalence of hypertension in newly presenting type 2 diabetic patients and the association with risk factors for cardiovascular and diabetic complications. *Journal of Hypertension, 11*(3), 309–317.

UKPDS 33. (1998). United Kingdom Prospective Diabetes Study 33: Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications with type 2 diabetes. *Lancet, 352*, 837-853.

UKPDS 38. (1998). United Kingdom Prospective Diabetes Study 38: Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes. *British Medical Journal, 317*(7160), 703-713.

UKPDS 40. (1998). United Kingdom Prospective Diabetes Study 40: Cost effectiveness analysis of improved blood pressure control in hypertensive patients with type 2 diabetes. *British Medical Journal, 317*(7160), 720-726.

US Department of Health and Human Services. (2010). Healthy People 2010, Volume 1: Health Communication. Washington, DC: US Department of Health and Human Services.

US National Center for Health Statistics and the Health Care Financing Administration. (1987). *ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification, Volumes 1, 2, and 3 Updates: Official Authorized Addendum, Effective October 1, 1987*.

Washington, DC: National Center for Health Statistics and the Health Care Financing Administration.

Ver Ploeg, M., & Perrin, E. (2004). *Eliminating health disparities: Measurement and data needs*. Washington, DC: National Academies Press.

Vinik, A. I., Maser, R. E., Mitchell, B. D., & Freeman, R. (2003). Diabetic autonomic neuropathy. *Diabetes Care, 26*(5), 1553.

Ward, M. M., Yankey, J. W., Vaughn, T. E., BootsMiller, B. J., Flach, S. D., Welke, K. F., et al. (2004). Physician process and patient outcome measures for diabetes care: Relationships to organizational characteristics. *Medical Care, 42*(9), 840.

Young, B. A., Katon, W. J., Von Korff, M., Simon, G. E., Lin, E. H. B., Ciechanowski, P. S., et al. (2005). Racial and ethnic differences in microalbuminuria prevalence in a diabetes population: The Pathways Study. *Journal of the American Society of Nephrology, 16*(1), 219.

Young, B. A., Maynard, C., & Boyko, E. J. (2003). Racial differences in diabetic nephropathy, cardiovascular disease, and mortality in a national population of veterans. *Diabetes Care, 26*(8), 2392.

Yusuf, S., Sleight, P., Pogue, J., Bosch, J., Davies, R., & Dagenais, G. (2000). Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *The New England Journal of Medicine, 342*(3), 145.

Zhang, X., Gregg, E. W., Cheng, Y. J., Thompson, T., Geiss, L. S., Duenas, M. R., et al. (2006). Correctable visual impairment among persons with diabetes - United States, 1999-2004. *CDC Morbidity and Mortality Weekly Report, 55*(43), 1169-1172.