

**ANALYSIS OF THE REMEDIES 4D CLINICAL TRIAL: A REDESIGN OF PRIMARY
CARE TO OVERCOME CLINICAL INERTIA AND IMPROVE OUTCOMES**

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ABSTRACT

Approximately 29.1 million, or 9.3% of the total US population, currently have diabetes and this number is predicted to increase to 48.2 million by 2050. As the prevalence of diabetes increases, the number of complications associated with diabetes will likely increase as well. Diabetes associated complications can lead to dysfunction or failure of a number of organ systems such as the cardiovascular, cerebral, and renal systems. The key to reducing diabetes complications is to control the patient's blood glucose, blood pressure, and cholesterol levels as well as providing preventative services. Fewer than 20% of people with diabetes have their blood glucose, blood pressure, and cholesterol levels adequately controlled. This is partly due to the failure to intensify diabetes treatments in a timely manner, also known as clinical inertia.

REdesigning MEDication Intensification Effectiveness Study for Diabetes (REMEDIES 4D) was a clinical study aimed at redesigning primary care to overcome this clinical inertia and improve patients' diabetes outcomes. Certified Diabetes Educators (CDEs) implemented pre-approved, evidence based, medication intensification protocols for a yearlong intervention. These analyses show that the REMEDIES4D intervention improved patients' blood glucose compared with the usual care group and those in the intervention were more likely to have their diabetes medication intensified; that clinician and medication satisfaction do impact medication

adherence and clinical outcomes; and, for these participants, there were no correlations between two measures of cognitive performance with medication adherence and HbA1c. This dissertation provided supporting evidence that CDEs in the primary care practice can improve patient's outcomes and since CDEs focus on clinical and behavioral factors, they can better support patients' behavioral and clinical goals. These findings are of public health significance since this model of care can be implemented in other community based primary care practices. In these practices, CDEs, a highly educated and underutilized resource, can work with primary care providers to better maintain people with diabetes clinical HbA1c goals, possibly reducing or delaying long term complications of diabetes and improving people with diabetes' quality of life.

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PREFACE

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1.0 INTRODUCTION

Diabetes is a category of related metabolic diseases that is characterized by elevated blood glucose levels (hyperglycemia) due to deficient insulin secretion, insulin action, or both. Hyperglycemia, if left untreated or uncontrolled, is associated with long term damage, dysfunction, or even failure of a number of organ systems including retinal, renal, nervous, and cardiovascular(1; 2). In order to reduce both acute and chronic complications and manage their chronic disease, people with diabetes require continuous care and self-management education(3). In addition to hyperglycemia, those with type 2 diabetes (T2D) are more likely to have elevated blood pressure and low density lipoprotein cholesterol (LDLc)(4)

T2D is one of the most common diseases in the world. In 2014, 387 million people were estimated to have diabetes and an additional 316 million individuals have impaired glucose tolerance, putting them at high risk of developing diabetes(5). By 2035, it is projected that over 1 billion people will either be at high risk for diabetes or living with the disease itself(5). In the United States, approximately 29.1 million people have diabetes, and this number is expected to rise to 48.2 million by 2050(6; 7). Additionally, in 2014, 4.9 million deaths globally were attributed to diabetes while in the United States, over 75,000 people died of diabetes(5; 6). However, in the United States, this number may be underreported as only about 35-40% of those with diabetes who died had diabetes listed on their death certificate, and only 10-15% of those

with diabetes who died had it listed as an underlying cause(8). Though the percentage varies, similar underreporting is seen in other countries such as Brazil(9).

The risk of mortality in people with diabetes is elevated compared with the general population. One study's results showed that those with type 2 diabetes have a 15% increase in all-cause mortality and a 14% increase in cardiovascular disease (CVD) death(10). Younger patients (<55 years of age) have a 92% excess risk of death, as compared with similarly-aged people in the general population, despite having their glucose controlled to 6.9% glycated hemoglobin (HbA1c) or less(10). Since this study was in Sweden, a country with universal healthcare, access to care was likely not a factor in the increased mortality among those with diabetes(10).

Mortality and complications can be reduced by controlling glucose, blood pressure, and lipids in people with diabetes. Every 1% reduction in HbA1c decreases the relative risk for microvascular complications by 37%, diabetes-related deaths by 21%, and myocardial infarction by 14%(11; 12). A 10mmHg reduction of systolic blood pressure decreases the relative risk of microvascular complications by 13%, diabetes related deaths by 15%, and myocardial infarction by 11%(13). The Scandinavian Simvastatin Survival Study's subanalysis of those with diabetes showed that use of statin therapies was associated with a 25% decrease in coronary heart disease and aggressive lowering of LDLc can be beneficial in those with diabetes(14).

Routine testing of clinical values, microalbuminuria, eye exams, and foot exams are also recommended to prevent and reduce complications in diabetes patients(3). The American Diabetes Association (ADA) recommends that blood pressure be tested at every doctor's visit, HbA1c at least twice a year, and LDLc annually, if levels are stabilized(3). ADA also

recommends an annual urinalysis and retinal eye exam for people with diabetes; feet should also be checked annually, as long as the feet are not insensate, deformed or ulcerated(3).

Despite the evidence illustrating the importance of controlling patients' clinical values, and routine testing, fewer than 20% of people with T2D had all of their clinical values at goal level and just over 50% of patients were on statins(4). The Translating Research into Action for Diabetes (TRIAD) study examined 8,000 insured patients with diabetes over a period of 3 years and found that 4.2% did not have an HbA1c, 11.6% did not have an LDLc, 6.9% were missing foot exams, 9% were missing eye exams, and 9.7% had no urinary albumin tests on file(15).

One reason behind these persistent gaps in clinical and preventative measures is clinical inertia. Clinical inertia is the failure to initiate or titrate treatment when necessary, or failure to perform a needed preventive service such as eye or foot examinations(16; 17). Repeated studies have shown that those with diabetes do not have their medications intensified despite having consistently elevated HbA1c values(18-20). A variety of reasons are used to explain clinical inertia: lack of time in clinic visits, prioritizing other health conditions, concern about medication costs, concerns about side effects, especially hypoglycemia in the case of insulin initiation are a few of the major ones(16; 19).

Clinical inertia, combined with a shortage of primary health care providers, who most people with diabetes see for their care, constrains an already overextended health care system(21). The Institute of Medicine recognizes how both of these factors can impact patient care; they recommend that research prioritize redesign strategies comparing the effectiveness of allied health providers for chronic conditions(22).

There is a small yet growing body of evidence that allied health care providers can support better quality of life and clinical outcomes when making medication changes

independent of the physician. The objective of this dissertation is to add to this body of evidence by analyzing the REdesigning MEDication Intensification Effectiveness Study for Diabetes (REMEDIES 4D). REMEDIES4D was a clustered, randomized, clinical trial, implemented by certified diabetes educators (CDEs), that addressed this gap, using evidence-based diabetes management protocols to deploy a systematic and effective redesign of current diabetes treatment approaches in primary care. This dissertation will focus firstly on the main results of the trial, analyzing if the intervention improved intervention participant's outcomes, compared with the usual care group. Secondly, the intervention's effect on medication and provider satisfaction, and if provider and medication satisfaction affects medication adherence and clinical outcomes, will be assessed. Lastly, the intervention group will be analyzed to see if increased cognitive scores have an impact on reduction in HbA1c or improvement in diabetes medication adherence, as well as which factors are associated with cognitive score increases and improvements in HbA1c and diabetes medication adherence.

2.0 DIABETES MELLITUS

Diabetes mellitus is a category of related diseases in which the person has prolonged high blood glucose levels. Diabetes mellitus is typically divided into three major categories: Type 1 Diabetes (T1D), Type 2 Diabetes (T2D), and gestational diabetes. In addition to these three subcategories, people with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) who do not have the entire suite of diagnostic criteria for diabetes are considered to have pre-diabetes(23). People with T1D, T2D, or gestational diabetes are at increased risk for complications and pre-mature death(24).

2.1 TYPE I DIABETES

2.1.1 Definition

T1D, formerly known as insulin dependent diabetes or juvenile diabetes, is a chronic autoimmune disease (24). With T1D, mononuclear cells invade the islets (small isolated mass of cells of one type), which causes an inflammatory reaction in the β -cells of the pancreas (25; 26). Over time, it is suggested that the inflammatory reaction induces enough stress on the β -cells that they go into apoptosis, programmed cell death (26; 27). Since pancreatic β -cells create, store, and release the hormone insulin, which is instrumental in the regulation of blood glucose levels,

(26) destruction of these cells impairs or eliminates the body's ability to produce insulin, leaving the person dependent upon external insulin treatment for the rest of their life (26; 27). Determination of β -cell destruction is marked by autoantibodies to islet cells, insulin, glutamic acid decarboxylase, and tyrosine phosphatases IA-2 and IA-2 β (25). One or more of these autoantibodies are detected in ~90% of individuals at the time of T1D diagnosis (25). T1D often develops suddenly, and the affected person experiences symptoms such as abnormal thirst, dry mouth, frequent urination, fatigue, constant hunger, weight loss, and/or blurred vision (5).

2.1.2 Epidemiology

In the United States, around 18,500 people younger than 20 years of age are diagnosed with T1D annually(6; 22). Around 1.25 million Americans live with T1D, 200,000 of who are under 20 years of age(6; 25). The overall estimated incidence rate of T1D in the United States is 24.3 per 100,000 person years(26). The incidence rates vary in the United States. For example, In Allegheny County, Pennsylvania the incidence of T1D is 18.2 per 100,000 person years, a lower rate may be explained by the fact that the incidence was assessed in the early 1990s (27). It is estimated by 2050, nearly 5 million Americans, 600,000 of who are under the age of 20, will be living with T1D(25). Worldwide, approximately 497,100 children under the age of 14 are living with T1D, a global rate of 26.1 per 100,000 children(5). An estimated 79,1000 children under the age of 14 are diagnosed each year(5). Between 1990 and 1999, the overall global incidence rate of T1D increased 3.0%(28) .

T1D can be diagnosed at any age. Up to 10% of adults who are initially thought to have T2D, have autoantibodies associated with T1D(29). Adult onset of T1D is typically associated with a slower rate of β -cell destruction and delayed dependency on insulin(29). Though it can be

diagnosed at any age, over 85% of worldwide incident T1D cases are diagnosed in those under the age of 20, making T1D primarily a disease of the young(29). Incidence rates typically increase from birth until around 14 years of age(28). Recently, studies of European diabetes registries have shown a marked increase in incident cases in those between 0 and 4 (30).

Roughly 80% of those with autoimmune disease are women; this characteristic female bias is not seen in T1D (31). In fact, T1D is the only major organ-specific autoimmune disease to not show an overall female bias(31). Globally, the boy/girl ratio is very close to 1 (28). If sex ratios are examined geographically, some variation appears. While most countries stay close to the global boy/girl ratio of 1, some like Sardinia show an excess male risk with a ratio of 1.5(28). In other countries, such as Venezuela, females have an excess risk of T1D(28). Even in the same country, there can be large variation in gender risk. For example, in Argentina, Corrientes reported that females have an excess risk of diabetes with a boy/girl ratio of 0.6 while in Tierra del Fuego males have an excess risk with 2.2 boy/girl ratio (28). In the United States, females have an increased risk of T1D with an incidence of 25.3 per 100,000 person years while males have a rate of 23.3 per 100,000 person years(26).

In the United States, non-Hispanic whites are at the highest risk for developing T1D with an incidence of 26.1 per 100,000 person years(26). Those of African American and American Indian descent have a slightly lower incidence of T1D with incidences of 25.4 per 100,000 and 25.0 per 100,000, respectively(26). Hispanic and Asian/Pacific Islander youth have the lowest incidence of T1D in the United States(26).

T1D accounts for only 5-10% of all cases of diabetes(22). It is difficult to talk about global T1D incidence and prevalence in generalities. This is due to large geographic variation in incidence among countries.(32) Incidence rates are grouped into five categories: very low (<1

per 100,000 /year), low (1-4.99 per 100,000 /year), intermediate (5-9.99 per 100,000/year), high (10-19.99 per 100,000/year), and very high (≥ 20 per 100,000/year)(28). In the majority of Asian countries, incidence was very low while African countries ranged from low to intermediate. South American countries ranged from very low to high (28). The highest incidence rates, except for Kuwait, are in Europe and North America(28).

The geographic variations in T1D incidence and prevalence have several possible explanations. First, is the quality and quantity of epidemiological data. Many countries in Africa, for example, have scarce epidemiological data regarding T1D due to fewer studies or poorer surveillance (out of 54 countries, only 5 African countries are included in the World Health Organization Diabetes Mondiale (DIAMOND) Project), under and misdiagnosis, and poor prognosis(5; 33; 34). Secondly, there is large disparity in T1D survival. In high income countries, T1D survival and prognosis was good (32; 35). In the United States, if a person with T1D does not develop renal disease, there is no excess 20 year mortality risk compared to the non-diabetic population (32; 35; 36). However, in low and middle income countries, survival is much more precarious (32). Lastly, one of the largest reasons for the difference in incidence is the multifactorial etiology of T1D.

2.1.3 Etiology

Like many chronic diseases, the etiology of T1D is multifactorial, still partially unexplained, and a rich topic for research.

Genetic

While the majority of those diagnosed with T1D occur in people who have no family history of the disease, T1D still has strong genetic factors.(32) People who have a first degree

relative with T1D have a 15-times greater lifetime risk of developing T1D compared with the general population.(32) Dizygotic twins have a concordance rate of 6-10% while monozygotic twins have a concordance rate greater than 60%(32). This evidence for genetic influence on the disease has led to T1D becoming one of the most intensely studied complex, multigenetic disorders.

The first genetic association reported for T1D was the human leukocyte antigen (HLA) region on chromosome 6p21.31, in the early 1970s.(41) After decades of intensive study of the HLA region, research has described odds ratios for specific DR-DQ haplotypes that range upwards of 11.(41) The HLA region is over 4Mb long, has a role in directing the immune response, and has been implicated not only in transplant rejection, but also in other complex autoimmune diseases such as rheumatoid arthritis and multiple sclerosis; infectious disease response such as in malaria and AIDS; and cancers such as Hodgkin's disease.(41) Combined with the fact that the HLA region is the most polymorphic region of the human genome, with >6543 unique allele sequences (as of July 2011), research of this complex region is still ongoing and its complexity is ever increasing.(41) The genes that are known to affect T1D susceptibility primarily are grouped in three general categories: immune function, β cell function, and insulin expression.(41)

Those who have the DR3/4-DQ2/8 heterozygous haplotype are the most susceptible to developing T1D(27). Even then, only 30-50% of those with T1D have this DR3/4-DQ2/8 genotype, which leaves a large percentage of the T1D population's genetic risk unexplained.(41) Data from recent studies illustrate that the proportion of T1D people with high risk HLA genotypes have been decreasing while the proportion of those diagnosed with T1D, with low risk or even protective HLA antigen, have begun to increase.(42)

While other areas of the genome have been associated with T1D risk, in over 40 years of research, none have been as strongly associated as the HLA region. So, while there is an undeniable genetic component to the T1D etiology, the complexities highlighted above show that genes do not always explain who does and who does not develop T1D. Clearly, there are other influential factors in T1D etiology.

Environmental

To explain why some people with genetic susceptibility develop T1D and others do not, studying the gene-environment interactions may be of some help. There has been much research into other risk factors and the possibility of precipitating events that may trigger T1D. In those who present with T1D in childhood, the average duration of the asymptomatic period is 2.5-3 years, although it can be as little as a few months to more than 20 years.(42) Migrant studies have supported the ideas of environmental triggers in T1D etiology in that populations that immigrated from areas of low incidence to areas of high incidence have higher incidence rates of T1D (42).

The DIAMOND Project had 105 centers in 53 countries that had sufficient data for analysis to determine if seasonality was associated with T1D diagnosis. (43) In many of the centers that reported data, there were statistically significant seasonal patterns in T1D diagnosis.(43) T1D, especially in adolescents, was significantly more likely to be diagnosed in the fall and winter months.(43) There is currently no clear reason why this seasonality exists, but it is thought that it may have to do with higher rates of viral infections that circulate in the winter months, a possible precipitating event of T1D.(27)

As with many other complex diseases, such as multiple sclerosis, there has been a wide range of precipitating events and other possible environmental triggers implicated in the etiology

of T1D. Viral infections, for example, have been implicated in T1D etiology for more than 100 years.(42) Enteroviruses are the main genus thought to trigger T1D(44). The two possible mechanisms through which viruses may trigger T1D development is either via direct cytolytic effect or persistent low levels of viremia that trigger the autoimmune disease process, which will then initiate β cell destruction.(42) Many studies of T1D have seen a close temporal association between enterovirus infection and the first appearance of T1D-associated autoantibodies. (42; 44-48) However, other follow up studies failed to find the same significant association, possibly due to lower enrollment and reduced statistical power or fewer testing time points.(42) Other viruses, such as rotavirus, mumps, and varicella, have also been implicated in triggering T1D but unlike enteroviruses, data is lacking. (49)

In order to help explain why some genetically-susceptible children develop T1D while others do not, a wide range of possible factors have been explored. Some, such as early exposure to infections from daycare, and routine childhood vaccinations, were not associated with an increased risk of T1D but rather, seemed to exert a potentially protective effect against T1D. (29) In a large European study, higher maternal intake of vitamin D during pregnancy was found to be protective against T1D, which was supported by a large separate Norwegian study.(29) Other factors, such as childhood vitamin D intake and early introduction of cow's milk, were found to be both protective or risk factors for T1D, depending upon the study(29; 50). Lastly, there are some factors that are possible candidates for being an environmental trigger, though more studies are needed. One study found that early introduction of gluten products (<12 months of age) increased the risk of β cell autoimmunity.(29) Interestingly, delay of gluten product introduction did not substantially reduce the risk for islet autoimmunity in genetically at risk children, showing that there may be a time sensitive period when gluten may impact T1D risk (29)

To complicate the study of environmental triggers even further, genetics need to be reintroduced into the discussion. First, as illustrated by the protective element of maternal vitamin D intake, but not childhood vitamin D intake, there is usually a limited age-window in which the environment can affect gene expression. Second, though not entirely clear, data support that the environmental factor that may trigger T1D manifestation depends upon which diabetic-susceptible gene a person has.(29) Early exposure to cow's milk to people with HLA=DR3/4,DQB1*0302,DR3/3 or DRX/4,DQB1*0302 is not associated with development of β -cell autoimmunity.(29) The HLA-DR3 allele, which is present in a high percentage of patients with T1D, is associated with viral persistence which may trigger β -cell autoimmunity.(29)

2.1.4 Mortality

Before the introduction of insulin therapy in the 1920s, a diagnosis of T1D was almost always a death sentence(51). Soon after insulin's introduction and dissemination, T1D mortality dropped so that 10 year survival was over 90%(51). Decades later, mortality due to T1D continues to drop, with each subsequent generation of those diagnosed with T1D outliving the first.(52; 53) In fact, in the absence of renal disease, those with T1D have the same 20-year mortality risk as the general population.(39; 40) The mortality rate for children with T1D is 0.63 per 100,000 children with T1D.(54) Like many other health issues in the United States, African Americans with T1D have a higher mortality rate compared to their white peers.(55; 56)

However, in middle and low income countries, the outlook for children with T1D is much poorer. Estimates can be hard to obtain as children often die before they can even be accurately diagnosed. (54) One study in Tanzania illustrated that 10% of patients "diagnosed" with cerebral malaria actually had pre-coma or coma due to uncontrolled T1D. (37) Even if

accurately diagnosed, the access to proper supplies such as clean needles, blood sugar monitors, and insulin, can be difficult. A survey of 25 African countries showed that in half of them, insulin was unavailable, even in large city hospitals, and only 20% of the countries had regular access to insulin in rural areas.(57) Even if insulin is available in these countries, the cost can be prohibitive. For instance, in many countries, T1D care can cost \$150-\$200USD, which is half to two-thirds the average yearly income of \$300USD.(37) Lack of access, combined with high cost of care, are two of the largest reasons for high T1D mortality in low and middle income countries(37). In many countries in sub-Saharan Africa, the life expectancy of a child newly diagnosed with T1D is around one year(37). In Bamako and Mali, a child can be expected to live around 8 years after diagnosis, while a child in rural Mozambique has a life expectancy of 7 months post T1D-diagnosis.(29; 37; 58; 59) While multifactorial, this is due largely to lack of access to insulin therapy, both in supply and prohibitive cost, and a health care system unable to diagnose and care for diabetic complications such as diabetic ketoacidosis(37).

2.2 PREDIABETES

2.2.1 Definition

Prediabetes, or intermediate hyperglycemia, (60). refers to people with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT)(61). Since prediabetes most often occurs before progressing into T2D, those with prediabetes will also have insulin resistance and impaired β -cell function, like T2D(61). Prediabetes is part of the insulin sensitivity period that can occur up to 13 years before T2D diagnosis(60). People who have been diagnosed with

prediabetes are in a high-risk state for development of T2D as 5-10% of people with prediabetes will progress to T2D every year(60). Also, people who meet the criteria for prediabetes are at an increased risk of not only diabetes but cardiovascular disease and overall mortality(62; 63).

2.2.2 Diagnostic Tests

Since those with prediabetes are asymptomatic, the American Diabetes Association (ADA) has criteria for testing those who are at high risk of prediabetes. Those at high risk includes adults who are overweight ($\text{BMI} \geq 25 \text{ kg/m}^2$ or $\geq 23 \text{ kg/m}^2$ in Asian-Americans) and have an additional risk factor such as physical inactivity, first degree relative with diabetes, diagnosed with hypertension, or hyperlipidemia, or a clinical condition associated with insulin resistance such as polycystic ovarian syndrome (64). All overweight or obese adults over the age of 45 should also be tested and if normal results are returned, they should be retested every three years(64).

Currently the diagnostic criterion for prediabetes is to be diagnosed with IFG or IGT or an HbA1c between 5.7%-6.4% is also considered diagnostic of prediabetes (64; 65). IFG is a fasting plasma glucose (FPG) of 100 mg/dL to 125 mg/dL(65). For IGT the diagnostic criterion with a 2-h plasma glucose value after a 75-g oral glucose tolerance test (OGTT) of 140 mg/dL to 199 mg/dL(65).

Each diagnostic test has its strengths and weaknesses when it comes to identifying patients with prediabetes. HbA1c is not considered by the ADA for diagnosing prediabetes in pediatric patients as it underestimates the prevalence of prediabetes in obese children and adolescents(66). For pediatric patients, the 2-h plasma glucose was the strongest predictor of prediabetes in pediatric patients regardless of age, ethnicity, and sex(66).

The prevalence of IGT and IFG can vary widely in a population, between ethnic groups, age ranges, and sex distribution(67). Studies have shown that OGTT and FPG tests do not pick up the same people. For example IGT is more frequent in females rather than males(67). When applying FPG to the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Asia (DECODA), one third of the population with diabetes and three quarters of the population with IGT per the OGTT would be considered normal if FPG was used(68). FPG was more likely to pick up younger patients regardless of ethnicity but in Asian populations FPG was less likely to diagnose obese patients while in European or southern hemisphere island populations, FPG was more likely to diagnose obese patients(68). The results of the OGTT is determined more by peripheral insulin resistance and is better at detecting the total burden of diabetes, diabetes in the elderly, and impaired IGT, which is more commonly associated with CVD risk factors and events(69).

2.2.3 Epidemiology

Like T2D, prediabetes is also an increasing health burden in the United States and around the world. Analysis of the National Health and Nutrition Examination Surveys (NHANES) for those ≥ 12 years of age illustrated that the age-adjusted prevalence of prediabetes in the United States between 1999-2002 was 27.4% and rose to 34.1% between 2007-2010(70). The prevalence was 51% when limited to US adults above the age of 65(6). In 2012, it was estimated that 86 million adults had prediabetes(6). The rise in prediabetes in the United States is largely attributed to the rise in obesity over the last few decades(71).

In US adults with prediabetes, the ethnic/racial breakdown is similar among non-Hispanic whites (35%), non-Hispanic blacks(39%), and Hispanics(38%)(6). Analyses of national

representative samples, such as NHANES data, have shown that there isn't a significant difference between ethnic groups(69; 71).

While prediabetes, like T2D, has been considered a disease of middle age, it has become increasingly common in young adults, adolescents, and even children(72). According to data from NHANES, the rate of prediabetes in youth increased dramatically from the 1999-2000 estimate of 7% to 16.1% in 2005-2006(73; 74). In pediatric populations who have other diabetes risk factors such as obesity, family history of diabetes, or hyperinsulinemia, the prevalence of prediabetes is even higher(73-75) US adolescent males have a 2.4-fold higher prevalence of prediabetes compared to their female counterparts(74). In adults over the age of 20, males were significantly more likely to have prediabetes (p-value=0.0002) with 35.7% of males diagnosed with prediabetes compared with 22.8% of females(69).

The countries with the highest prevalence of prediabetes are China and India(72). About 15.5% of the total adult Chinese population is estimated to have prediabetes, around 148.2 million(72). Asia, Africa, and the Gulf region of the Middle East are emerging hotspots for prediabetes(72). In 2010, the International Diabetes Foundation projected that the number of adults with prediabetes was expected to increase to 472 million by 2030 with the greatest absolute increases expected in southeast Asia and the western Pacific regions(60).

2.2.4 Treatment

The primary reason for treating prediabetes is to prevent or delay progression from prediabetes to T2D(60). One of the most effective ways to treat prediabetes is lifestyle interventions that encourage an increase in physical activity and healthier eating habits(76). Lifestyle interventions reduced the incidence of T2D by 58% compared to the placebo group (76;

77). The US Diabetes Prevention Program (DPP) reported that weight loss was one of the most important determinants of risk reduction and that for every kilogram of weight a participant lost, their risk of developing T2D decreased by 16%(78). The DPP was a large and fairly diverse study with 58% of participants identifying as non-Hispanic white(78). Lifestyle interventions have also been found to be beneficial in Finnish and Japanese populations(77; 79).

Besides lifestyle interventions, which can be difficult to maintain, some pharmacological interventions have also been beneficial in reducing the rates of progression from prediabetes to T2D. In the DPP, metformin reduced incidence of T2D by 31% compared to placebo(76). Thiazolidinediones have also been shown to reduce the incidence of T2D. In the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) Trial, 50% of participants in the rosiglitazone group converted to normoglycemia compared to 30% in the placebo group ($p\text{-value} < 0.0001$)(80). Pioglitazone reduced the risk of conversion to T2D by 72% compared to placebo but was associated with significant weight gain and edema(81). The STOP-NIDDM trial assessed the effect of acarbose in preventing T2D conversion and found that significantly fewer people randomized to the acarbose group converted to T2D and significantly more reverted back to normoglycemia(82). Similar results were also found in a Japanese trial that studied the use of voglibose to reduce incidence of T2D in a high risk population.

2.3 TYPE 2 DIABETES

2.3.1 Definition

T2D, formerly known as adult onset diabetes or noninsulin dependent diabetes, is a chronic health condition that refers to individuals who have relative insulin deficiency or insulin resistance(83). While pancreatic β -cell dysfunction occurs, unlike T1D the dysfunction is not due to autoimmune destruction (25; 84). Loss of β -cell function is due to other factors like inflammation, elevated glucose and cholesterol levels, amyloid, and oxidative and endoplasmic reticulum stress(85). Progressive deterioration of glucose tolerance over a period of several years is characteristic of T2D development(86). During this time period people progress from normal glucose tolerance to impaired glucose tolerance before developing diabetes, when insulin secretion and insulin action abnormalities worsen while endogenous glucose output increases(86). The ADA recommends using one of following three blood tests to diagnosis T2D: HbA1c, FPG, OGTT (23). An HbA1c $\geq 6.5\%$, FPG ≥ 126 mg/dL, or a two-hour OGTT ≥ 200 mg/dL are considered to be diagnostic of T2D(23; 24). If hyperglycemia is not unequivocal it is recommended that the criteria are confirmed with repeat testing(24). In addition to the previous criteria, the World Health Organization also considers random plasma glucose ≥ 200 mg/dl in the presence of classic diabetes symptoms to be diagnostic of diabetes(24; 33).

2.3.2 Epidemiology

Globally, T2D accounts for 90% of diabetes cases (25). Currently, 11% of adults over the age of 18 in the United States and 27% of those over the age of 65 are living with T2D(85).

In 2012, 1.7 million new cases of T2D were diagnosed in Americans 20 years of age or older, a rate of 7.8 cases per 1,000 people(6). In Allegheny County, Pennsylvania, 9% of adults reported a diagnosis of T2D(87). In a 2010 report, Allegheny County is one of ten counties that had a significantly lower diabetes mortality rate, compared to the overall Pennsylvania rate(88). However, the Healthy People 2010 goal was to reduce the age-adjusted diabetes (both underlying and contributing causes) death rate to 45 or fewer per 100,000 people and in 2007 the age-adjusted diabetes death rate was 70.0 per 100,000, about 55% higher than goal(88).

In the 1930s, data from the United States National Health Interview Survey showed that females over the age of 40 were nearly two times more likely to be affected by diabetes than males (34). Nearly two-thirds of diabetes cases at this time were in females(34). By the 1980s, the rates for males and females were very similar with 2.7 males per 100 were diagnosed with T2D and 2.9 females per 100(1). At the turn of the 21st century, the rate for diabetes in males began to increase at a much higher rate than in females(1). In the 31 years from 1980 to 2011 the rate of diagnosed diabetes increased 156% to 6.9 per 100 while females increased 103% to 5.9 per 100(1). If the T2D sex ratio is examined geographically, some variation appears. In the late 1990s, globally there was an excess of females to males with diabetes (73 vs 62 million) but revised estimates in a 2004 paper showed that globally the ratio changed so that the sex specific prevalence were similar(41; 55). While some populations such as Canada, Ghana, Nigeria, and South Korea have similar male prevalence in T2D, other areas such as Cameroon, Uganda, and Kuwait favor females (52; 54; 57; 89). Some countries such as Guinea or Mali show no sex bias in diabetes.(54)

Unlike T1D, T2D has traditionally been a disease of adulthood. In 2011, the average age of diagnosis in the United States was 53.8 years of age with the median age slightly higher, at

54.2 years of age(90). Since 1997, the average and median ages of T2D diagnosis in the United States have remained largely unchanged, only fluctuating up two or three years(90). Increasingly over the past years, more and more cases of T2D are being diagnosed in Americans under the age of 20(72). Two decades ago, T2D accounted for less than 4% of pediatric diabetes diagnoses but in some ethnic and racial groups, such as American Indian, T2D is above 80% of new pediatric onset diabetes (35; 72).

The racial disparity of T2D seen in pediatric diagnoses continues into adulthood. In the United States, approximately 8.7% of Non-Hispanic Whites were estimated to have T2D (43). Compared to Non-Hispanic Whites, other racial and ethnic groups are disproportionately represented(43). The National Institute of Diabetes and Kidney Disease estimates prevalence rates of T2D are 9.5% for Hispanic/Latinos, 13.3% for Non-Hispanic Blacks , and 15.1% for American Indians/Alaska Natives(43). However, the use of racial and ethnic categorization in T2D prevalence can be viewed as problematic and obscuring(42). The current racial/ethnic categories used are very broad and can obscure the vast differences within group(42). The Diabetes Study of Northern California (DISTANCE) study is a good example of this in regards to Asian/Pacific Islanders(45). While the aggregated Asian and Asian/Pacific Islanders categories had similar overall T2D estimates of 12.2 and 12.3%, respectively, within each category prevalence varied dramatically(45). Pacific Islanders were at highest risk with a T2D prevalence of 18.3% and a risk ratio (RR) of 2.43 when compared to Non-Hispanic Whites and the lowest was Chinese with a prevalence of 8.2% and a RR of 1.14(45).

In 2010, over 250 million people had T2D and that number is projected to rise to nearly 400 million by 2030, 7.7% of the global adult population(72). According to the International Diabetes Federation, the numbers are worse with a 2014 report suggesting 387 million people

currently have T2D and will increase to nearly 600 million by 2035(5). Part of the reasons that the numbers vary is due to the underdiagnosis of diabetes. Approximately one in two people living with diabetes (179 million) are undiagnosed(5). In low to middle income countries, particularly in sub Saharan Africa, up to 90% of those with T2D are undiagnosed(5). Over three-quarters of the world's T2D live in low and middle income countries, with the largest number in the Western Pacific with 138 million people with T2D(5).

With increasing industrialization and a longer-lived population, the prevalence of T2D has rapidly increased in every country and region in the world, doubling over the past three decades (72). The rise in people living with T2D is also largely attributed to the global rise in obesity(72). Though obesity is a substantial risk factor in the development of T2D, the etiology of T2D is more complex than obesity-induced.

2.3.3 Etiology

Genetic

Though T2D is commonly thought of as a purely lifestyle-induced disease, like T1D, T2D also has components of heritability. One of the greatest risk factors for developing T2D is obesity but not all obese people develop T2D, in fact fewer than 20% of obese individuals become diabetic and some people with T2D have normal body weights(46). This suggests that there is more to etiology of T2D than lifestyle factors.

In twin studies, monozygotic twins have a concordance rate between 50 and 92% while dizygotic twin's concordance rate is around 37%(46). In adult non-twin sibling pairs, the concordance rate for T2D was 11%, significantly higher ($p\text{-value} \leq 0.0001$) than the spouse pairs' (used to evaluate the relative contribution of lifestyle factors versus genetic ones) concordance

rate, which was 2.8%(91). When examining parent-child pairs, those who have a parent with T2D have a ~40% lifetime risk of developing T2D, though the risk is higher if the parent with T2D is the mother, and a risk approaching 70% if both parents have T2D(92).

Glucose homeostasis is known to be heritable and families who are at increased susceptibility for T2D have higher heritability estimates for impaired fasting glucose, pancreatic beta cell function, and features of insulin resistance syndrome(47). Other features of insulin resistance syndrome, like body mass index (BMI), blood pressure, and serum lipid levels have also been reported as having high heritability(46). The inheritability of these metabolic phenotypes have been reported in European, Japanese-American, Pima Indian, Hispanic American, and African American populations, which suggest that there is a genetic factor in the etiology of insulin resistance syndrome and T2D(47; 93-96).

Even though there has long been circumstantial evidence suggesting a genetic component to T2D, identifying the genetic variants that conferred increased risk of T2D has been a formidable challenge (97). In the mid-1970s one prominent geneticist, James V. Neel, referred to the discovery of T2D genetic factors as “the geneticist’s nightmare,” a prediction that up until 10 years ago had proven accurate(98). In the past few years, partially due to the advances in molecular technology, over 65 genetic variants that increase the risk of T2D have been identified and described(92). However, untangling the genetic variants for T2D still remain extremely difficult.

Of the genetic variants discovered, most of them only moderately increase risk of T2D, by 10-30%(92). Additionally, the majority of variants are noncoding variants so the functional consequences of the variants are difficult to investigate(92). The functional variants that have been identified regulate insulin secretion in insulin-sensitive tissues but not insulin action(92).

The genetic components that have been identified thus far do not improve models that predict T2D risk when other risk factors, such as total triglycerides and HDL cholesterol, are accounted for(92). Unlike T1D's more predictive HLA region, genetic testing for T2D has shown to have little clinical relevance (92).

Lastly, there is a current theory of 'thrifty' genes that can have long lasting impact on a person's weight and subsequent health, including possibly predisposing them for T2D(99). The theory is that these genes were valuable in our early ancestors by favoring the economical use and storage of energy in times of famine(99). These genes would have favored glucose use in the brain, diverting it from the muscles, during times of starvation instead of using the glucose(99). Now that, at least in much of the Western world, food is plentiful and calorie dense, these genes may be maladaptive and contribute to obesity, insulin resistance, and T2D(99). Some of the current genes considered to be 'thrifty' are associated with fatty acid metabolism (AACS), gluconeogenesis(PCK1), glucose metabolism (NPY1R), and insulin processing (CPE) among others(99). Also, these genes are thought to interact with the environment and their phenotype is not solely based on genetic penetrance. 'Thriftiness' is thought to be affected by the fetal environment and less than optimal nutrition in utero will lead to the activation of these genes(100). This is based on a suite of obesity research and the fact that people who were born small for their gestational age were more likely to be obese and develop T2D(100). The theory of 'thrifty' genes is still under great debate as it is difficult to conclusively prove or disprove.

Since the current genetics of T2D have a poor ability to discriminate the genetic risk from the environmental or the interaction of gene and environment, it is crucial to recognize the environmental contributions of T2D. Until better T2D risk genes are found or technology

improves in order to identify relative gene contributions to risk, knowing environmental factors is one of the best ways to predict T2D risk.

Environmental

One of the key modifiable environmental/lifestyle factors for the etiology of T2D is obesity; the majority of patients with T2D are obese. The recent global epidemic of obesity largely explains the dramatic increase in T2D that has been seen in the last 20 years(101). Where a person's fat accumulates influences a person's risk for T2D just as much as the degree a person is obese(101). Increased visceral adiposity, located inside the peritoneal cavity that sits between internal organs and the torso, is associated with CVD and T2D while thus far, there is no evidence suggesting the subcutaneous adiposity confers the same risk(101). The reason why visceral adipose tissue increases risk while subcutaneous does not is not completely certain, but one possible mechanism is that visceral adipose tissue produces more proinflammatory cytokines, such as tumor necrosis factor alpha, which can induce insulin resistance(102). In addition to proinflammatory cytokines inducing insulin resistance, there are two additional mechanisms. First, is ectopic fat deposition, especially in the liver, and dysmetabolic sequelae and the second is mitochondrial dysfunction, which could decrease insulin sensitivity and compromise β -cell function(101). Whatever the mechanism, accumulating evidence suggests that even modest weight reduction can improve glycemic control and reduce T2D risk (101; 103-106).

Obesity, while arguably the most influential risk factor, is not the only environmental risk factor for T2D. Smokers, even former smokers, have an increased risk of developing T2D(107). A systematic review of 25 prospective cohort studies (N=1,200,000) showed a statistically significant increased risk for T2D in both active and former smokers(107). Consistent with the

dose response phenomenon, former smokers had the lowest risk with an RR of 1.23, lighter smokers (<20 cigarettes a day) with an RR of 1.29, and heavy smokers with an RR of 1.61 compared with non-smokers(107). Unlike obesity, there is some debate as to whether smoking is causal or if it is just a hallmark of an unhealthy lifestyle that may increase risk of T1D. Smoking does meet several of Hill's criteria for causation as smoking precedes development of T2D (temporal), those who smoke more are more likely to develop T2D (dose-response), smoking is a widely-reported significant risk factor (consistency), T2D is not negligible in the context of tobacco research (strength of association), and some studies suggest that smoking may lead to inadequate compensatory insulin secretion responses and has a clinically significant effect on oral and intravenous glucose tolerance tests (biologically plausible)(107-109).

Other

Approximately 135,000 pregnant females each year in the United States develop gestational diabetes(GDM)(110). While this number is rising, some believe it to be artefactual as more females are having their plasma glucose tested than before(111). Females are now screened for GDM between 24 and 28 weeks of gestation(111). The risk for GDM increases for pregnant females who smoke during pregnancy, drink during pregnancy, and are heavier(111). Babies born to females with GDM are more likely to be pre-term and be large for gestational age and have higher birth weight(111). Females with GDM are at higher risk of developing gestational hypertension and pre-eclampsia and have increased risk of developing T2D later on in their lives (110; 111). It is estimated that females who develop GDM have approximately a 70% increased risk of subsequently developing T2D, though numbers vary depending upon study and duration of follow-up(112).

Polycystic Ovarian Syndrome (PCOS) affect 6-10% of premenopausal Caucasian females and, like T2D, is both genetic- and obesity-related(113). Females with PCOS have a higher prevalence of insulin resistance and one study showed that 15.7% had impaired glucose tolerance(IGT)(113). In BMI-matched studies, females with PCOS have an odds ratio of 4.0 for developing T2D (95% CI 1.97, 8.10) compared with control females(113; 114). In other BMI matched studies, there is an epidemiological link between PCOS and T2D that is independent of obesity(113). A recent analysis of a cohort of 6000 Australian females, including 500 with PCOS, suggests that females with PCOS are 5 times more likely to develop T2D(115).

2.3.4 Mortality

Diabetes-related deaths may occur as the result of an acute crisis like a hyperglycemic crisis, which caused over 2,000 deaths in the United States in 2010, or from long term complications (6). People with T2D have a 1.7 greater risk of dying from cardiovascular disease than those without diabetes, even when adjusting for age(6). In some areas, cardiovascular deaths account for more than 50% deaths due to T2D (5). Overall, those with T2D have a 1.5 greater risk of dying in general compared to their peers without T2D (6).

Diabetes is currently the 7th leading cause of death in the US; it is listed as the underlying cause of death on over 75,000 death certificates each year. This number is also believed to be under-reported, with evidence from an examination of death certificates showing diabetes was included as a secondary factor on almost 250,000 death certificates in the US (6). An examination of death certificates in which diabetes was mentioned as a cause of death but was not the main cause, the number increases to nearly a quarter of a million deaths in the United States, and even then that number may be underreported(6). Worldwide, in 2012, 5.1 million

deaths were caused by diabetes, over 80% of which occurred in low and middle income countries(5; 116). By 2030, the World Health Organization anticipates that diabetes will be the 7th leading cause of death worldwide(117).

In Africa, more than 75% of diabetes deaths occur in those under age 60 years; this is almost three times higher than occurs in Europe (28%)(5). Southeast Asia and Middle East/North Africa regions have the next highest burden of premature diabetes deaths, with 55% and 50%, respectively(5). In the Western Pacific, over 15% of all deaths in those aged 20-79 were attributable to diabetes(5). There is little sex disparity in terms of mortality except in the Middle East/North Africa and Western Pacific regions, where females experience a higher proportion of deaths, but this disparity is likely due to the fact that males are more likely to die from other, non-diabetes related causes, such as armed conflict(5). From 2011 to 2013, there has been an 11% increase in deaths attributed to diabetes globally(5). While some countries report a decline in some non-contagious diseases, no country has reported any decline in diabetes mortality(5).

The wide disparity in diabetes-related mortality is largely due to lack of access to healthcare and relatively low healthcare expenditure(5). The North American/Caribbean region, which has the second lowest diabetes mortality rate in those under 60, spent the most, with 263 billion dollars in 2013(5). In comparison, Africa, which has exactly twice the diabetes-related mortality rate of the North American/Caribbean region in those under 60, spent only 4 billion dollars in 2013(5).

2.4 DIABETES COMPLICATIONS

Many diabetes complications are related to the severity and duration of hyperglycemia (118). The variety of complications can be acute or chronic and physiological or psychological.

2.4.1 Acute Complications

A few acute diabetes complications tend to be severe and can be life threatening. Diabetic ketoacidosis (DKA) is an acute life threatening complication that occurs when there is not enough insulin to process glucose, leaving fat as the primary source of energy(119). The use of fats instead of glucose causes a buildup of acidic ketone bodies, altering blood acidity(119). Though more typically seen in patients with T1D, those with T2D can also develop DKA(120). The most common causes of DKA are infection, under-treatment or nonadherence, and it occurs most frequently in those undiagnosed or newly diagnosed with T1D(120). DKA can lead to diabetic coma or death, largely from sepsis or pulmonary and cardiovascular complications(120).

Hyperglycemic hyperosmolar syndrome (HHS), unlike DKA, is more commonly seen in people with T2D(121). A typical patient with HHS is older, between 55 and 70, does not have a diabetes diagnosis, and is usually a nursing home resident(121). HHS is characterized by dehydration, hyperglycemia, and hyperosmolarity without any significant ketoacidosis(121). Like DKA, HHS can be severe and life threatening and is usually precipitated by infection, with pneumonia and urinary tract infections as the most common causes, or acute crises such as myocardial infarctions or a cerebrovascular events(121).

While hyperglycemia contributes to DKA and HHS, hypoglycemia (i.e., plasma glucose <70 mg/dl) is also a life-threatening complication in people with diabetes, especially in T1D.

Hypoglycemia is often subclinical, especially when hypoglycemic episodes are common(122; 123). Palpitations, extreme hunger, sweating, and confusion/difficulty thinking are common symptoms of hypoglycemia(123). If not corrected, hyperglycemia leads to more severe effects including seizure, coma, or even death(123). Besides these short term effects of hypoglycemia, repeated episodes can increase the risk of a cardiovascular event(122). When the brain becomes glycopenic, it can lead to an upregulation in counterregulatory hormones, such as adrenomedullary adrenaline and norepinephrine, which may induce an arrhythmia and increase cardiac load(122). During hypoglycemia, other circulating inflammatory markers increase, including C-reactive protein, interleukin 6 and 8, and tumor necrosis factor- α , which can result in endothelial injury or coagulation abnormalities(122).

2.4.2 Chronic Complications

2.4.2.1 Microvascular Complications

One of the most common microvascular complications is diabetic retinopathy, where the eyes are affected by progression of T2D(118). Retinopathy is generally divided into either background or proliferative retinopathy. In background retinopathy, the small vessels in the retina develop microaneurysms which can also cause lipid deposition and retinal edema. These changes are detectable with a dilated eye exam, but are usually first noted by the patient as seeing “dots” in the visual field(118). With proliferative retinopathy, the body tries to compensate for the vascular damage by creating new blood vessels on the retinal surface. These fragile new vessels, however, often penetrate into the vitreous, leading to hemorrhaging of the vitreous fluid. If not treated, proliferative retinopathy will eventually cause blindness.(118) Macular edema, where an increase in extracellular fluid within the retina alters the retinal

structures and reduces vision, is one of the most common retinopathies associated with diabetes(124). Adults with a history of at least 20 years of T1D are significantly more likely to develop diabetic retinopathy compared with adults with a history of T2D of the same duration in all categories except macular edema(125). Globally, approximately 34% of people with diabetes have any retinopathy, 7% have proliferative retinopathy, 6.8% have macular edema, and 10% have vision threatening diabetic retinopathy(125). For patients with proliferative diabetic retinopathy, the risk of blindness can be reduced by timely photocoagulation laser, vitrectomy, and careful follow-up(126).

Another organ system that is commonly damaged in diabetes is the kidneys, called diabetic nephropathy. Between 20-30% of all diabetics will develop any of the nephropathies(127). Microalbuminuria, defined as having a urinary protein concentration between 30 – 299 mg/24 hours, will develop in 12% of T1D patients within 7 years of their T1D diagnosis (118). Without any intervention, microalbuminuria will progress to macroalbuminuria, defined as a urinary protein concentration between 300-499mg/24 hours, and then further progress to overt diabetic nephropathy.(118) Between 20 to 40% of T2D patients with microalbuminuria will progress to overt nephropathy(127). By 20 years after overt nephropathy onset, approximately 20% of those patients will progress to end stage renal disease(127). Renal function can be preserved or improved by controlling hypertension, an important risk factor for diabetic nephropathy, often by placing a person with diabetes on an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker(128). Kidney complications can also be slowed by controlling blood glucose(65). Even with treatment, kidney disease can progress and lead to dialysis or kidney transplant(65). In the United States, diabetic nephropathy is the leading cause of kidney failure(118).

The nervous system can also be damaged by diabetes; this is called diabetic neuropathy. Diabetic neuropathy most commonly affects the peripheral nerves, manifesting as reduced peripheral sensation, such as loss of sensation of light touch, vibration, and temperature, or as tingling and pain.(118) While peripheral neuropathy can affect virtually any nerve, the median, ulnar, and radial nerves are the most commonly affected and the cranial nerves are infrequently affected.(118) Peripheral neuropathies greatly increase the risk of ulcerations and amputations of the extremities.(118) At least 20% of adult patients with a history of diabetes will present with a diabetic neuropathy(129). This number increases to about two-thirds of patients when subclinical diabetic neuropathy is taken into account(130). To date, the best way to prevent, delay, or slow the progression of diabetic neuropathies is through glycemic control(131).

Diabetic neuropathy can also affect the autonomic nervous system, i.e., autonomic neuropathy, and this is occasionally classified as a macrovascular complication(132). Autonomic neuropathy, can cause significant morbidity and even mortality in patients(65; 118). Autonomic neuropathy complications can range from erectile dysfunction and gastric issues, such as constipation, silent ischemia, and sudden cardiac death(65; 118). The best ways to treat autonomic neuropathy are by targeting glycemic control, the organ system affected by the neuropathy, or pain management(65; 118). Due to the wide range of manifestations that are categorized as autonomic neuropathy, prevalence estimates range widely, from 1.6% to 90%, depending upon the test used, population examined, type, and stage of disease(129). Between 43-87% of those with T1D have genitourinary bladder dysfunction and women with T1D have a fivefold greater risk of voiding difficulties compared with women without diabetes(129). Men

with diabetes are at greater risk of erectile dysfunction, with greater duration of diabetes positively associated with increased risk of erectile dysfunction(133).

2.4.2.2 Macrovascular Complications

Macrovascular complications are typically long term complications that manifest after years with the diabetes(65). As with most other diabetes-related complications, the occurrence/severity of macrovascular complications can be reduced by controlling glucose, lipid, and blood pressure levels(134). While cardiomyopathy and heart failure have been described as being associated with T1D, the incidence of these are relatively rare(135; 136). Coronary heart disease (CHD) is one of the leading causes of death in those with diabetes(137). While other CHD risk factors may be comorbid with diabetes, data suggests that diabetes is an independent risk factor for CHD(137); people with T2D have a 2-4 increased risk of coronary heart disease(134) while those with T1D have a hazard ratio for major CHD events about 10 times greater as compared with an age- adjusted general population(132). Not only is diabetes an independent risk factor for CHD, but when compared with people without diabetes, those with diabetes who suffer from a myocardial infarction are more likely to receive a poorer long-term prognosis, such as an increased risk of congestive heart failure, and death(137). A Finnish study found that, over 7 years, the risk of a first or second myocardial infarction (MI) was much higher in people with vs. without T2D; for those without a prior MI, the 7-year incidence of a 1st MI was 20.2% in the T2D population as compared with 3.5% in the non-diabetic group. Among those with a prior MI, 45% of T2D patients experienced a 2nd MI over 7 years, compared with 19% of those without T2D.(134).

While cerebrovascular disease in those with T1D is much rarer in comparison to CHD events, it is still important(132). According to results of the European Diabetes Study

(EURODIAB), the incidence rate of cerebrovascular events in T1D was 0.74%, much higher than that of the general population, at 0.2-0.3% per year(132). In patients with T2D, CVD is the leading cause of morbidity and mortality. Patients with T2D have a higher risk of stroke, earlier onset of symptoms, and worse outcomes(138). The Honolulu Heart Study reported that men of Japanese descent with diabetes have a relative risk for ischemic stroke of 2.45 compared with their nondiabetic peers(138). In 2005, a similar relative risk for ischemic stroke of 2.4 in patients with diabetes was reported in the Hemorrhagic Stroke Project(138). About 50% of people with T2D who survive a cerebrovascular event will have a long term disability(138). It is estimated that 20% of patients with diabetes will die of a cerebrovascular event(138).

Peripheral artery disease (PAD) includes several components such as “occult disease, assessed by ankle-brachial index, extremity arterial calcification, and lower extremity non-traumatic amputation”(132). The prevalence of PAD is difficult to ascertain since few patients will complain of intermittent claudication. Furthermore, the presence of peripheral neuropathy may mask the symptoms of claudication(139). Large studies report the prevalence of PAD ranges from 8% to 33% in people with diabetes(139). One study found an identical prevalence of PAD regardless of diabetes type while another reported higher prevalence in those with T2D(140; 141). Most data for PAD in T1D is focused on amputation. Non-traumatic amputation is high in the T1D population, ranging from 0.4-7.2% per year(132). In Sweden, by the age of 65, 11% of women and 20.7% of men with T1D have had a non-traumatic lower extremity amputation(132). In the US, while the rate of lower-leg amputations decreased between 1990 and 2010 by 51%, the number of lower leg amputation cases increased by 22,703 to 73,000 amputations due to the increased burden of diabetes (142). People with diabetes have a 10-times higher risk of amputation, and PAD was present in 94% of those who had an

amputation(143). Age and male sex are the largest risk factors for amputation(143). Risk of amputation and PAD can be reduced by glycemic control along with routine podiatric care and noninvasive vascular testing(144).

2.4.2.3 Other Physiological Complications

Diabetes does not just affect the vascular system of the body. People with T1D, especially adults who have had the disease for many years, also develop musculoskeletal complications such as (145) cheiroarthropathies, limited joint mobility, and periarticular thickening of the skin of the hands (a well described complication that can lead to significant and painful morbidity)(145). Cheiroarthropathy is defined as the presence of any one of the following musculoskeletal issues: adhesive capsulitis, carpal tunnel syndrome, flexor tenosynovitis, Dupuytren's contracture, or a positive prayer sign(145). In a cross-sectional analysis of over 1200 participants with T1D, 66% had current cheiroarthropathy, which was associated with worse Disabilities of the Arm, Shoulders, and Hand (DASH) functional disability scores(145). Like microvascular and macrovascular complications, cheiroarthropathies are associated with longer disease duration and poorer glycemic control (145). While the previously-described musculoskeletal complications can be seen in those with T2D, they are far more likely to be seen in those with T1D, as it is a disease of longer duration(146). Those with T2D are more likely to develop diffuse idiopathic skeletal hyperostosis and osteoarthritis though this is thought to be due more to the fact that many T2D patients are obese, rather than to having T2D itself (146).

People with T1D and T2D are, respectively, at 6.94 and 1.38 higher risk of fracture compared with the general population(147). The increased risk of fractures in people with T1D versus those with T2D is most likely related to their bone mineral densities (BMD)(147; 148).

People with T1D have lower BMD and long term bone loss, though the mechanism for this is not entirely clear(148; 149).

2.4.2.4 Psychological

Along with physiological complications, those with T1D also experience a higher burden of psychiatric disorders. In a cross-sectional study of adolescents with T1D, 37% of the population had a mood, anxiety, eating or behavioral disorder, with several having more than one diagnosis(150). The previously described psychiatric burden is much higher than associated community samples(150). Similar results have been reported in other studies(151). Suicidal ideation is also much higher in adolescents with T1D as opposed to their non-diabetic peers(152). However, even though ideation is higher, the rate of suicide attempts is comparable to that of the general population(152).

Psychiatric illnesses in those with T1D have been associated with poorer glycemic control(151). The association between poorer glycemic control and psychiatric illnesses is not poorly understood, but it is thought that the poorer control may be associated in general with adolescence, when metabolic control has a tendency to deteriorate(153). Also, psychiatric illnesses lead to a deterioration of self-care behaviors, such as noncompliance, which then can cause poor glycemic control(153).

Similar statistics have been seen in those with T2D. The prevalence of depression in the non-diabetic population is 17%, while in those with diabetes of similar age, the prevalence is 24%(154). A meta-analysis of 42 studies implicated that the presence T2D doubled the person's odds of comorbid depression(155). Patients with T2D who have been diagnosed with depression have significantly lower quality of life compared to their non-depressed T2D peers(154). People with T2D and comorbid depression tend to have poorer control of various clinical measurements,

such as cholesterol and triglycerides(156). A meta-analysis of 24 studies illustrated that, similar to what is noted among depressed people with T1D, depressed people with T2D also have poorer glycemic control and higher rates of hyperglycemia(157).

People who were diagnosed with T1D in childhood show evidence of generalized brain atrophy and ventricular enlargement, and exhibit cognitive changes like psychomotor slowing and poorer executive function as compared with their non-diabetic peers(158; 159). Whether the pattern of gray matter atrophy noted in middle-aged adults with childhood-onset T1D (insert citation) may lead to future development of dementia remains to be studied (160). The need for such work is further supported by results obtained from this same middle-aged T1D cohort; investigators observed a higher-than-expected prevalence of clinically relevant cognitive impairment (28%), which was related to chronic hyperglycemia, higher BMI, and prevalent microvascular disease (161).

T2D is well-established as a risk factor for dementia. A large cohort study in Rotterdam, of over 6,000 persons, found that the T2D attributable risk for dementia was 8.8%(162). A diagnosis of T2D almost doubled a person's risk of developing dementia and Alzheimer's Disease(162). Those who were treated with insulin were at the highest risk of dementia, possibly because they had a more severe case of T2D, or perhaps longer duration(162). A meta-analysis of 14 longitudinal population based studies also supports a T2D contribution to dementia(163). There are many possible pathophysiological mechanisms by which T2D can initiate or promote dementia, most of which revolve around hyperglycemia(163). Hyperglycemia can lead to vascular damage in the brain or can cause premature aging due to glucose toxicity(163). T2D may also interfere with amyloid metabolism, leading to Alzheimer's type pathology(163).

3.0 QUALITY OF CARE

3.1 DEFINING QUALITY OF CARE

Researchers define ‘quality of care’, in a number of ways. Some are generic, such as excellence (164), or expectations or goals which have been met(165) while others are more complex or multi-dimensional (166). For example, in 2001, the Institute of Medicine (IOM) released a report called ‘Crossing the Quality Chasm: a new health system for the 21st century’ which, in addition to criticizing the American health care system’s inability to provide consistent, high quality medical care to their patients, said that the system should aim to be safe, effective, patient-centered, timely, efficient, and equitable (22). While the variety of definitions each have their advantages and disadvantages, one of the most frequently cited definitions is the IOM’s which states, “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge” (167). For the purposes of this section, the definition of quality will follow the IOM definition.

3.2 THE RESEARCH GAP IN DIABETES CARE QUALITY

In 2012, 117 million American adults had one or more chronic health conditions(168). Unlike acute episodic care, such as influenza or injury, the effective treatment of chronically ill patients is a collaborative process between the providers and the patient with joint development of care strategies and targets and active follow-up (169). In the last decade and a half there has been unprecedented focus on quality from both researches and policymakers at all levels of government (170). Repeatedly, the concept that chronic care should consist of evidence based medicine and keep up to date on current treatment strategies is in the forefront(170). While this may be seen as common sense by some, the reality of implementing evidence based medicine is much more difficult.

Since the 1960s the amount of biomedical research and knowledge has increased dramatically (22). Currently, Medline indexes >560,000 new articles every year and Cochrane Central adds 20,000 clinical trials, a vast increase from the just over 100 trials approximately 40 years ago (22; 171). These growing numbers, and increasingly complex studies, are reflected in the number of drugs, medical devices, and other technologies that have been developed over the years(22). In the early 1980s, about 19 drugs were approved annually by the Federal Drug Administration (FDA) and by 2014, the number of drugs approved reached 44 (172), (22). There is an abundance of research being conducted but a lack of clinical implementation.

The process of moving information from research to real-world application is called translational research and this happens in two general stages(173). The first is “bench to bedside”, when laboratory research is moved into clinical research applications, such as testing new hyperglycemic medications, e.g., insulin, in clinical trials(173). The second is moving the knowledge from the clinical research setting to real-world applications; for example,

implementing new hyperglycemic medications is now part of the average provider's standard of care (173). In diabetes research, it is the second phase, from clinical research to the real world, where there is great stagnation. Large clinical trials such as the Diabetes Control and Complications Trial (DCCT) and U.K. Prospective Diabetes Study (UKPDS) have shown that tight glycemic and blood pressure control greatly reduce the risk of diabetes complications(11; 174-177). More recent studies, such as the Action to Control Cardiovascular Risk in Diabetes (ACCORD), illustrated that tight glycemic and blood pressure control need to be balanced with other risk factors and that controlling a patient's HbA1c to normal HbA1c (i.e. below 6%) or their systolic blood pressure to less than 120mmHg was more harmful than beneficial(178). Other trials, such as the Diabetes Prevention Program (DPP), illustrated that the benefits of a healthy diet and exercise, combined with metformin, can prevent or delay the development of T2D in people with impaired glucose tolerance(162; 179; 180). Despite DCCT ending in 1993 and UKPDS ending in 1997, fewer than 20% of people in the US with diabetes had their glucose, blood pressure, and lipid levels well-controlled in 2010 (4).

There are a variety of barriers to implementing new science into the clinical setting. Some are relatively easy to address, such as lack of provider knowledge about new methods of care, while others are more complex such as lack of patient insurance, financial disincentives, cultural misunderstandings, and underutilization of information technology(173). Roadblocks are often attributed to the provider but can occur at all levels such as patient, health care organization, and community(173). Translational research must be flexible as no single best practice is appropriate for all clinicians and the communities that they serve(173). Unlike research, where protocols must be strictly adhered to and the patient eligibility is tightly controlled, translating research to the 'real world' must be flexible and address issues such as

patient diversity, provider time constraints, reimbursement issues, history and politics of individual organizations, and systematic problems(173).

Support for translational research has become increasingly more popular in academic and research communities (181). Begun in 2006 and fully implemented in 2012, the Clinical and Translational Science Awards (CTSA) program was founded by the National Institutes of Health (NIH) to support a nationwide consortium of medical research institutions that will work together to advance the translational research process(182). The CTSA was formed to bring together experts from a diverse set of fields, such as biostatistics and research oversight, to redesign the translational model of research(183). Importantly, the CTSA also constitutes an educational program to train future researchers and foster inter-institutional collaborations(183).

3.3 CLINICAL GAP IN DIABETES CARE

While addressing gaps in health care research and quality of diabetes care, there is another large issue of care that needs to be considered: clinical inertia. Clinical inertia is the failure to initiate or titrate treatment when necessary or the failure to perform a needed preventive service, such as eye or foot examinations (16; 17; 184). Clinical inertia can have a heavy burden on a patient with diabetes. Numerous studies show that good glycemic control can reduce a person's risk of developing renal failure, neuropathy, and other microvascular and macrovascular complications (18), yet the solution to achieving treatment intensification and full access to preventive care services remains elusive.

When a provider fails to intensify needed medication for hyperglycemia, patients' glucose remains elevated, increasing their risk for complications (18). With people being

diagnosed at a younger age and living longer with T2D, failure to control glycemic levels and other risk factors could render their cumulative risk burden unmanageable (18). An eight year-long prospective, population based study of over 7,000 people with T2D showed that even in a well-controlled population, the average patient still spent nearly 5 years with an HbA1C >8.0% from diagnosis before being put on insulin therapy and 10 years with an HbA1C >7.0% (18). Another large cohort study at the Veteran's Administration (VA) showed that clinical inertia occurred in 68% of clinic visits among patients with an HbA1C >8% (185). Another study in a population receiving primary care in an academic medical center found that clinical inertia occurred in 58% of adults with an HbA1C \geq 8%, and in 57% of patients with a LDL \geq 100 mg/dl (185).

In addition to a failure to initiate and intensify therapies, other gaps in clinical care occur. In order to delay or prevent complications from diabetes, awareness of levels of risk factor control is needed. This awareness comes from the measurement of these risk factors.(64). According to the ADA 2015 Standards of Care, patients should have a lipid panel conducted at diagnosis and then routinely, every 1 to 2 years, or at the provider's discretion, until the patient's lipid levels has stabilized (64). While patients should routinely monitor their blood glucose at home, HbA1C tests should be performed *at least* two times a year in patients who are meeting treatment goals or have stable glycemic control(64). In patients who are not achieving their glucose goals or are not stable, HbA1C tests should be ordered quarterly until the patient becomes stable or begins to meet treatment goals (64). The Translating Research into Action for Diabetes (TRIAD) study examined over 8,000 insured patients with diabetes from 10 different health plans over a period of three years to identify persistent gaps in care, or clinical inertia, on several preventative measures, including HbA1C and LDL measurements(15). For the purposes

of this study, a persistent gap was defined as a patient not having a service done for the entirety of the three-year study period(15). While only 4.2% of people did not have any HbA1C tests performed, 11.6% did not have any lipid panels done in the three years of the study(15).

In order to prevent the development or progression of diabetes-related complications, other preventative services should also be conducted, such as microalbuminuria testing, eye exams, and foot exams (64). According to the ADA guidelines, people with diabetes should have their eyes examined upon diagnosis and, if there is no evidence of retinopathy, they should be re-examined at least every two years for monitoring; if evidence of retinopathy exists, patients should be examined at least annually to monitor any potential progression (64). To assess kidney function and to monitor for kidney disease, all patients with T2D, regardless of duration, should have their urinary albumin tested at least once a year, while patients with kidney disease should have their renal function tested at the provider's discretion (64). Foot examinations are another important preventative service for patients with diabetes;(64). An annual comprehensive foot exam can identify risk factors that may predict ulcer or amputation(64). However, patients who have feet that are insensate, deformed, or ulcerated should have their feet examined at every visit to their physician (64). The TRIAD study also examined the three above-mentioned preventative strategies and found that, while only 6.9% were missing a foot exam, 9.0% were missing an eye exam, and 9.7% did not have their urinary albumin tested for all three years(15). In total, 22% of patients were missing at least one of the five needed services during the three year period(15). Even though all patients were insured, those who were more likely to have a persistent gap tended to be of lower socioeconomic status, with shorter diabetes duration, to be taking fewer medications, and have poorer health behaviors(15).

Up-to-date treatment strategies will not be very effective if they fall victim to clinical inertia. Though clinicians prefer to blame the patient for clinical inertia for their non-adherence to medication, research suggests that approximately 75% of the responsibility for clinical inertia is due to the inaction of the physician, and only 25% is due to patient resistance or refusal(186). Patient adherence is a separate issue from clinical inertia, as it does not explain why physicians fail to titrate therapies or advance new ones (186). There are a variety of reasons suggesting why a physician may not intensify treatments: lack of time in clinical visits, prioritizing other health conditions, concern about medication costs, concerns about side effects, especially hypoglycemia in the case of insulin initiation, or lack of knowledge of current treatment guidelines(185; 186). Prioritizing other health conditions, or competing demands, is a major concern in primary care(187). The more concerns a patient has during a visit is associated with a 49% decrease in the likelihood of medication changes, independent of encounter length or previous HbA1C(187). Additionally, patients with higher HbA1Cs have shorter durations between scheduled appointments, leading to more opportunity for medication changes(187). While competing patient demands is a possible legitimate reason not to intensify a patient's medication when indicated, it is only one for short term inertia and does not explain the consistent prolonged gaps in medication intensification. A study in Canada showed that patients waited 9.2 years after diagnosis to be started on insulin therapy, even though their mean HbA1C was 9.5% at the time of insulin initiation, suggesting long term inability to meet glycemic goals(188). A retrospective cohort study involving more than 80,000 patients also showed significant delays in intensification. Patients with an $HbA1C \geq 8\%$ waited, on average, 1.6 years to see intensification of an additional oral anti-hyperglycemic drug, while those with a lower HbA1C yet who had still not achieved control had a median of 2.9 years before drug intensification(189). The delays

were even longer for those taking more than one oral anti-hyperglycemic drug, with a median of 6.9 years for those with an HbA1C \geq 8% and up to 7.2 years for those with a lower, but still not at target, HbA1C(189).

While providers have a limited amount of time to interact with a patient during an office visit, at least one study found little evidence that more productive physicians deliver needed preventative care more than their less productive colleagues, suggesting that time spent with the patient may not be as large a component as is perceived (190). As for cost, in settings such as VA hospitals and public health clinics, where medication costs should be less of a concern, there is still evidence of clinical inertia(190). While side effects of a drug may be of concern, it does not explain why a patient who is already on a lower dose of a drug does not have their dosage titrated as needed(17). A survey of 71 primary care physicians found that, even though they agreed their patients would benefit, two-thirds did not start their patients on insulin sooner because they thought it would be too burdensome on the patient(191). The reason for delaying initiation of insulin therapy does not seem to lie in a concern about hypoglycemia, since 97% of the physicians said that they would be willing to put their patients on insulin if it did not involve the use of needles(191). Lastly, a study of 370 primary care providers from three states found that these clinicians were able to identify 88% of patients with well-controlled diabetes, and 94% of patients with poorly-controlled diabetes, thus showing that they were up to date with current standards of care guidelines(192).

If there is evidence to suggest that many of the reasons that are cited as to why clinical inertia happens are incorrect, then why does clinical inertia happen? A paper by Phillips et al. in 2001 suggested several different reasons as to what may cause clinical inertia, including overestimation of care provided and ‘soft’ reasons to avoid intensification of therapy(17). Both

residents and practicing physicians have overestimated their adherence to current guidelines in regards to hypertension and lipid management, cancer screenings, and assessing cardiac risk factors (17). The same survey of 370 physicians, discussed above, also asked them how often they provided the needed services such as foot or eye exams, or ordered tests such as HbA1C or urinary albumin for their patients with diabetes(192). In these areas, the physicians' self-reported frequency of conducting these measures were quite high, in contrast to patient self-reports and analysis of large claims databases(17). As for 'soft' reasons, referring back to the survey of physicians regarding insulin initiation, many physicians were concerned with how their patient would react when approached to initiate insulin, or were concerned that insulin initiation reflected a failure on their part to control their patient's diabetes, while 38% of physicians found insulin therapy to be too time consuming(191). A larger study of >3000 providers had similar results, with the majority of providers delaying insulin therapy until deemed absolutely necessary(193). None of listed reasons above are adequate ones for failure to initiate insulin therapy. While studies or surveys of physician behaviors are relatively few, a study by El-Kebbi (year), assessing barriers to provider adherence to diabetes-management protocols, found that for a group of patients in which control was poor and therapy was not advanced, the reasons physicians did not intensify treatment were that 1) the patients' control was improving, and 2) their numbers were caused by dietary nonadherence(194). The average time between visits for this group was 2-3 months, and the majority of this group were obese, suggesting that this group had sufficient time to achieve a glycemic steady state and that poor diet was unlikely to be a novel factor in the patients' lifestyle(194)

4.0 CHANGING STATE OF PRIMARY CARE

Traditional primary care practices were organized to respond to acute and urgent medical problems, not to provide long term preventive care for any particular illness(195). Providers would diagnose and treat the issue at hand and, in doing so, the patient's role was largely a passive one, especially since the full clinical course was usually a matter of days or weeks, not years(196). With the population of the US aging, becoming more sedentary, and more obese, Americans have become "sicker", with more than one-half of American adults diagnosed with at least one chronic disease(168; 195). While the health care expectations and needs of Americans have expanded and changed, the model of care for primary care has not kept pace.

Primary care in the last 20 years has become more comprehensive, with the addition of more preventive measures, such as adult hepatitis and pneumococcal vaccinations and breast and colon cancer screenings (195). Problems previously thought of as "social", e.g., depression, substance abuse, domestic violence, now demand the primary care provider's attention (195). In regards to diabetes care, routine tests such as HbA1c did not exist before the 1980s, and neither did care guidelines such as annual eye exams, lipid level management, or urinary albumin tests(195). Also during this time, patients with hyperglycemia but who were not ketotic, spent several days in the hospital to receive treatment and diabetes education, whereas now, the expectation is that such patients would seek treatment and education in ambulatory or home settings(195). Currently, in this system designed for brief encounters and acute illnesses,

primary care providers are expected to provide quality comprehensive and preventive care to their patients with chronic illnesses, at least 50% of whom have more than one of chronic conditions(168; 195-197). Even in a health care system as specialty-centered as in the US, there is still great reliance on the primary care. Generalists provide 85% of care for patients with chronic obstructive pulmonary disease, 82% for hypertension, and over 90% of people with diabetes receive care from their primary care provider(21; 195).

The ever expanding comprehensiveness expected of primary care is only one of the major concerns facing primary care today. Another issue facing the field of primary care is the decline in primary care physicians. Between 1997 and 2005, the number of medical students seeking residencies in family care practices dropped by nearly 50%(198). In a system that values specialists, especially in the realm of compensation, where once 50% of internal medicine students sought to be specialists in 1998, by 2006, 80% of internal medicine students became specialists(198). The increased specialization by physicians is expected to result in a shortage of generalists and by 2025, the shortage is estimated to be between 40,000 and 52,000(199).

4.1 CHRONIC CARE MODEL

Recognizing the growing comprehensiveness of primary care, the increasing number of patients with chronic illnesses, the previously discussed inability to adequately provide care for those with chronic illnesses, and the current and projected shortage of physicians, new models of care have been suggested. One of the most influential models is the Chronic Care Model (CCM), developed in the late 1990s by Edward Wagner(200). The CCM constitutes a redesign of the primary care practice that takes place within three overlapping communities(197). The first is

within the entire community, with its numerous public and private policies; the second is the health care system itself, especially in regards to reimbursement; and the third is the provider organization(197). Within these three realms, there are six elements that Wagner identified as essential for improving patient outcomes: self-management support; decision support; delivery system design; clinical information systems; an informed activated patient; a prepared proactive team(201).

The CCM emphasized the use of coordinated multidisciplinary healthcare teams (202). Multidisciplinary teams can include a number of different individuals, e.g., nurses, social workers, pharmacists, all of whom are there to support the patient and supplement the primary care provider. For example, a patient with diabetes could receive self-management support services from a case manager, a service shown to enhance clinical outcomes (203; 204). There are many ways that the CCM can come together to utilize the varied skills of the team, such as treatment planning, evidence-based clinical management, self-management support, more effective consultation, and sustained follow-up(202).

Intervention strategies that utilize the healthcare team approach as advocated by the CCM are associated with better outcomes(202; 205). Complementary team members improve professionals' adherence to guidelines, clinical and health status, and patient satisfaction(202; 205; 206). Though the use of the CCM is encouraging, there is some evidence that the team falls apart if the physician cannot effectively share patient care, and that the cost effectiveness of this model needs further study(202; 205; 207).

4.2 PATIENT CENTERED MEDICAL HOME

The CCM became the foundation for one of the latest trends in US healthcare, the Patient-Centered Medical Home (PCMH). The PCMH evolved from the CCM in 2007, largely because adoption of the CCM did not involve the needed reimbursement changes, this led to a disparity between those who implement the CCM and those who receive the financial benefits(208; 209). The PCMH, which has been endorsed by payers, professional societies, and policymakers, focuses on having a continuous healthcare relationship with the patient(210). This relationship includes evidence-based care that is measured for continuous safety and quality improvement(210). While the PCMH may seem conceptually straightforward, there are a number of obstacles that can delay its implementation. A PCMH practice requires a “whole practice transformation”, not incremental changes, since many of the components of the PCMH are interrelated(210; 211). As with the CCM, technology is a key component of establishing the PCMH, therefore the current lack of integration of electronic health care records (EHR) and the cost of implementing new software hinder the development of PCMH(210; 211). Additionally, the PCMH requires that physicians shift their approach: instead of the common authoritarian leadership, physicians must facilitate a team approach and delegate responsibilities to the healthcare team(210).

The Affordable Care Act prominently supported the PCMH framework by establishing a Center for Medicare and Medicaid Innovations, the agency that created the Multipayer Advanced Primary Care Practice Demonstration, covering 1200 PCMHs and over one million beneficiaries(208; 209). An evaluation of over 10,000 diabetes patients in Southeastern Pennsylvania who received care from a PCMH illustrated significant improvements in the percentage of patients who received complications screenings and who were on therapies to

reduce morbidity and mortality(209). There were also modest, but statistically significant, improvements in clinical parameters such as blood pressure and cholesterol levels(209). Other PCMH, or proto-PCMH, demonstrations in diabetes care show similar encouraging results(212). The Community Care of North Carolina, where care coordination is assisted by care managers and there is regular reporting of quality measures, reported improvements in HbA1c, blood pressure, and LDLc parameters, so that all three measures were above National Committee for Quality Assurance (NCQA) recommendations(213). They also reported reductions in emergency room visits and hospital admissions, with an estimated cost savings of over \$160 million(212; 213). Similarly the Colorado PCMH Pilot, where care coordination was assisted by care managers and there was regular reporting of quality measures as well as patient registries and practice coaches, reported reductions in emergency room visits and hospital admissions as well as improved patient and health care workers satisfaction(212; 214).

4.3 ANCILLARY STUDIES

Previous research shows that diabetic patients treated by allied health care providers, such as nurses or pharmacists, achieve better glycemic, blood pressure, and cholesterol control(215-223). For example, a community-based trial in California allowed pharmacist to provide pharmacotherapy modifications, laboratory monitoring, dietary and physical activity recommendations, diabetes self-care education, and specialist referrals, as compared with usual practices(221). In the intervention group, HbA1c improved significantly more, from 9.5% to 6.9%, than the usual care group, whose HbA1c was reduced from 9.3% to 8.4%(221). Patients in the intervention group also were more likely to attain reductions in LDLc and blood pressure

(221). The intervention group's 10-year risk of CHD was reduced from 16.4% to 9.3% while the control group's was reduced from 17.4% to 14.8%(221). In Tennessee, a pharmacist was added to the diabetes health care team; pharmacists saw patients independently, with the physician, or worked with physicians to develop patient care plans(224). In this study, HbA1c was reduced, on average, by 1.16%, and the proportion of patients who achieved their HbA1c goal increased significantly, from 12.75% to 36.76%(224).

In Los Angeles, an integrated model using specially-trained pharmacists and nurses to deliver diabetes care following detailed protocols and algorithms under the supervision of a diabetologist, was implemented. In this model, diabetes complications screenings were carried out more frequently compared with the usual-care group, as well as the intervention group having a 3.5% reduction in their HbA1c compared with a 1.5% reduction in the usual-care group. (218). Patients with diabetes who receive care from nurse case managers, including self-management education and implementation of diabetes guidelines, had significant improvements in blood pressure measurements, in emotional distress scores, and in the frequency of screenings for diabetes complications(220). Care teams that integrated allied health care providers consistently demonstrate their ability to effectively and safely improve patients' clinical measurements (216; 217; 224; 225). While the allied health care provider integration approach may not always lead to significantly better clinical outcomes. In the DREAM 3 trial, where both the nurse centered group and the primary care provider control group saw significant reductions in blood pressure throughout the study but there was not a significant difference between the nurse centered and primary care provider groups, there has not been evidence to suggest that their care is substandard relative to the usual care a patient may receive(226). The utilization of allied health care providers in primary care improves patient outcomes because these providers

can overcome two of the most common barriers to treatment intensification: time, and clinical inertia(222).

4.4 CERTIFIED DIABETES EDUCATORS

Diabetes self-management training has long been considered an important part of clinical management(227). Diabetes education aims to optimize metabolic control and quality of life while seeking to prevent acute or chronic diabetes complications(227). The main source of education for people with diabetes is through trained, certified health professionals known as Certified Diabetes Educators (CDEs)(228).

Certification for diabetes educators began in 1986 and by 2006, more than 12,000 health care professionals were currently certified(229). Since its inception, the CDE has evolved into more complex, educational management and now also plays a role in medical/medication management(229). CDEs possess comprehensive knowledge of, and experience in, prediabetes, diabetes prevention, and disease management; they educate and support people with diabetes in understanding and managing the condition and promote self-management to achieve treatment and behavioral goals to optimize patient health(230).

CDEs fill a crucial role in diabetes care. Primary care providers tend to offer advice on risk reduction instead of provide education and skills that will affect behavior change, something a CDE is trained to do. Managing diabetes is complex, as a patient needs to attend to multiple disease process. Given the time limitations inherent in primary care, many diabetes patients may not be receiving the education and training that they need(231). The Center for Disease Control and Prevention (CDC) recognized the crucial nature of diabetes self-management education, and

the importance of CDEs, when setting their Healthy People 2010 goals(231). The percentage of people with diabetes who have any sort of diabetes education is low: in 1994, 35.1% had any sort of education while in 1998, only 40% had contact with a CDE(232; 233). The Health People 2010 goal was to increase this percentage to 60%(231); information regarding this goal has yet to be released by the CDC.

Primary care is an ideal setting for CDEs to work individually with diabetes patients (234). Results of a meta-analysis show that CDEs, and the self-management education they provide, decrease a patient's HbA1c by an average of 0.76% more than a control group after first contact, and this effect continues during follow-up visits(235). Moreover, increased contact with a CDE increased the effect of HbA1c reduction(235). However, only 13% of CDEs work in the primary care setting, largely due to issues with space and reimbursement(234). In the Pittsburgh Regional Initiative for Diabetes Education (PRIDE) study, a CDE was deployed to primary care practices to provide Point-Of-Service diabetes education(236). The 784 patients that received CDE attention had a significant decrease in HbA1c and LDL levels(236). Another study delivering CDE provided self-management education not only improved the patient's HbA1c, LDLc, empowerment, and knowledge, but also increased the provider's adherence to the ADA's Standards of Care process measures(237).

5.0 SUMMARY

Diabetes is an increasingly common chronic disease that affects millions of people worldwide. Of the subtypes of diabetes, T2D remains the most prevalent, accounting for 90% of cases(238). In 2014, an estimated 387 million people around the world were estimated to have T2D and this number is projected to rise to nearly 600 million by 2035(5). Currently, 11% of adults in the United States, and 27% of those over the age of 65, are living with T2D(85). Though prevalence numbers vary due by region, there is no doubt that T2D represents a significant public health burden.

While prevention and etiological studies remain a crucial element in slowing the T2D pandemic, the care that people with diabetes receive must also be a focus of attention. In the United States, many patients with diabetes are not treated to goal levels, nor do they have the appropriate preventative exams performed as routinely recommended(4; 15). Control of clinical measures, such as HbA1c, blood pressure, and LDLc, and routine preventative exams are crucial in delaying or preventing complications of diabetes(12; 14; 178). Diabetes complications are associated with long term damage, dysfunction, or even failure of a number of organs/organ systems, including the eyes, kidneys, heart and nerves(1; 2) These complications can severely impact people with diabetes' quality of life, and often lead to premature death(6).

The concept that relates to missed opportunities to provide needed services or to appropriately intensify medication is called clinical inertia(17). Although clinical inertia is not

unique to people with diabetes, studies have shown that those with diabetes can spend nearly 5 years with an HbA1c>8.0% and 10 years with an HbA1c>7.0% from time of diabetes diagnosis to start of insulin therapy(18). The TRIAD study showed that in an insured population, 4.2% of diabetes patients did not have an HbA1c test in the three years of the study, even though biannual testing is recommended for *controlled* glycemia (i.e., more frequently for uncontrolled glycemia)(3; 15). In total, 22% of patients were missing at least one needed services in a five year period(15). Clinical inertia has been repeatedly found in large population studies, the VA, and in insured populations(15; 18; 185).

There have been a variety of reasons given for clinical inertia: e.g., competing demands; not enough time during the visit; concern on medication costs(185; 186). Though these reasons are legitimate in the short term, they do not explain the chronic clinical inertia noted above. They also do not explain why in Canada, a country with universal health care, patients waited 9.2 years after their diabetes diagnosis to start insulin therapy, despite having a mean HbA1c far above goal(188).

Since the late 90s, the model of primary care has shifted focus to a more team based, collaborative, patient centered model(201; 204; 207). From the Chronic Care Model to the Patient Centered Medical Home, use of allied health care providers to assist the primary care provider in patient care has been suggested(201; 204; 207; 212). Studies have shown that when allied health care providers, such as pharmacists or nurses, manage diabetes care and are able to make pharmacotherapy modifications, patients' quality of life and clinical values improve(218; 221).

Certified Diabetes Educators (CDEs) are a highly educated yet under-utilized workforce in primary care(230). Studies show that the education and support that CDEs provide are

effective in improving diabetes care(228). A meta-analysis found that CDEs and the self-management education they provide decreases a patient's HbA1c on average by 0.76% more than a control group's HbA1c after first contact and continues to decrease a patient's HbA1c during follow-up visits(229). Another study delivering CDE-provided self-management education not only improved the patient's HbA1c, HDLc, empowerment, and knowledge, it also increased the provider's adherence to the ADA's Standards of Care process measures(231). Placing CDEs in the primary care setting, where they can implement standardized, pre-approved, evidence-based protocols to intensify treatment, using a patient-centered approach, has the potential to improve people with diabetes's clinical values. Improved clinical values can lead to fewer diabetes complications and improvements in people with diabetes' quality of life.

6.0 METHODS

6.1 OBJECTIVES AND SPECIFIC AIMS

Although adequate treatment of hyperglycemia, hypertension, and hypercholesterolemia can reduce morbidity and mortality in people with diabetes, the current system of care delivery fails to adequately treat these patients. Physicians delay intensification of anti-hyperglycemic drugs and insulin initiation, leaving patients in poor glycemic control for years(189). Additionally, though recommended by the ADA, fewer than 50% of patients with diabetes have been placed on a statin. With the increasing prevalence of diabetes, the number of complications will also continue to rise, burdening an already overburdened health care system(4). Considering that >80% of adults with diabetes seek diabetes care from primary care practices, new care delivery strategies focused in primary care settings are needed(19).

REdesigning MEDication Intensification Effectiveness Study for Diabetes (REMEDIES 4D) is a clustered, randomized, clinical trial that aims to deploy a systematic and effective redesign of current diabetes treatment approaches in stand-alone primary care practices in southwestern Pennsylvania. Patients in practices randomized to the intervention group received diabetes care and medication intensification from a CDE, following an evidence-based algorithm. Patients in practices randomized to the control group (usual care) continued to

receive usual care from their physician as well as attend monthly diabetes support groups with a CDE. Study aims were to:

1a) Determine if those who received care using the REMEDIES4D protocol (intervention group) had improved clinical outcomes (HbA1c, blood pressure and LDLc) compared with those in the usual care group.

1b) Assess differences in treatment intensification of those in the REMEDIES protocol group compared with those in the usual care group.

Hypothesis: Those who received the REMEDIES4D intervention will have better clinical outcomes (A1C, blood pressure and LDLc) compared with those in usual care, and will also be more likely to have their medications intensified.

2a) Determine if those who received care using the REMEDIES4D protocol experienced increased clinic and medication satisfaction.

2b) Determine if clinic and medication satisfaction impact medication adherence and clinical outcomes (A1C, blood pressure, and LDLc).

Hypothesis: Those who receive the REMEDIES4D intervention experience an increase in clinic and medication satisfaction which positively affects their clinical outcomes (A1C, blood pressure, LDLc) compared with the usual care group.

3) Determine if cognitive status impacts medication adherence and clinical outcomes (A1C, blood pressure, LDLc).

Hypothesis: Lower cognitive performance is significantly associated with patient adherence to medications and their ability to improve clinical outcomes compared with those with higher cognitive performance.

6.2 STUDY DESIGN

6.2.1 Overview

REdesigning MEDication Intensification Effectiveness Study for Diabetes is a multi-practice, clustered, randomized, clinical trial that took place in non-academic, stand-alone, primary care practices in Allegheny, Butler, and Westmoreland counties in Pennsylvania.

6.2.2 Population

After approval from the University of Pittsburgh Institutional Review Board, participant recruitment began in late 2012 and continued until February 2014. In order to be considered eligible for the study, participants had to be over the age of 18; diagnosed with T2D for at least one year; visited their primary care physician within the last 12 months; and have at least one of their most recent clinical values for HbA1c ($\geq 7\%$), blood pressure (SBP ≥ 140 mm/Hg or DBP ≥ 80 mm/Hg), or LDLc (≥ 100 mg/dL) above goal. Patients who were not ambulatory; had gestational diabetes, were pregnant or planning on becoming pregnant in the next year; were moderately or severely cognitively impaired; had a scheduled surgery; were on dialysis; or were not able to read or comprehend English were excluded from the study. In total, 240 participants consented to the study, 175 in the intervention group and 65 in the control group.

Demographic characteristics, including age, sex, race, education, and income, as well as medical ones, such as duration of diabetes, smoking status, HbA1c, blood pressure, and LDLc values, were collected. Except for race, HbA1c, diastolic blood pressure, systolic blood pressure, and depression severity, there were no significant differences between groups. The

intervention group had more racial diversity; was more likely to have moderately severe depression; and was more likely to have higher HbA1c values compared with the control group. The control group was more likely to have higher diastolic and systolic blood pressure values and more likely to have severe depression scores compared with the intervention group.

6.2.3 Setting

All primary care practices owned by the University of Pittsburgh Medical Center that had at least fifty patients with T2D and had an electronic medical record system were considered eligible. Thirty-four practices were contacted in early 2012, with a goal of enrolling twenty practices. If practices declined to participate, more were contacted until eventually, fifteen practices agreed to participate. After agreeing to participate, the principal investigator, the CDEs, and the study coordinator met with the providers(s), office managers and staff to discuss the study and review the informed consent. Once informed consent was obtained from each physician within the practice, they were stratified into one of three groups, according to the number of patients with diabetes in the practice (under 200, 200-500, greater than 500). After stratification, practices were randomized, by flip of a coin, to either intervention or usual care. Practices were stratified so that a more balanced patient recruitment may be achieved.

All practices were located in southwestern Pennsylvania, in Allegheny, Butler, and Westmoreland counties. Of the fifteen practices, three were urban while the rest were suburban. All but one of the practices had more than one provider, and two-thirds of the practices had nursing staff. All of the practices had medical assistants, clerical support, and access to a case manager. None of the practices had certified diabetes educators (CDEs) working in the practice though diabetes education programs were available at local hospitals.

6.2.4 Intervention

The REMEDIES4D intervention is based around the use of allied health care providers employing evidence-based diabetes care protocols. These protocols were derived from the work previously done by Mayer Davidson(218), ADA Standards of Medical Care(65; 239-241), Standards for Diabetes Self-Management Education and Training(242), American Association of Clinical Endocrinologists Guidelines(243), National Cholesterol Educational Program Adult Treatment Plan III(244), and Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 and 8(245; 246). Prior to implementation, the protocols were reviewed by the primary care providers participating in the study who were encouraged to provide feedback about the protocols which were presented to the medical director for the study, Dr. Francis Solano. The protocols were updated throughout the trial as evidence changed. The protocols were also altered to provide lower-cost alternatives if medication cost was a concern, as well as alternative therapies for those unable to tolerate statins. Any medical issue, such as depression or neuropathy, which fell outside the purview of the REMEDIES4D protocol, was referred to the participant's primary care provider for follow up.

Participants randomized to the intervention group had a 12-month long intervention period. The participants had one-on-one research visits scheduled with the CDEs at baseline, and then at 3 months, 6 months, and 12 months after baseline. At the baseline visit, participants had their blood pressure taken, received a foot exam, and had a review of their medical history. The first research visit lasted approximately two hours. At every clinical visit, clinical values were assessed, and any gaps in care, such as eye exams or lab tests, were addressed and subsequently ordered. Following the REMEDIES4D protocol, the participant's hyperglycemia, hypertension, and hypercholesterolemia medications were reviewed and, if required, changed

accordingly. All orders were written by the CDE and sent to the primary care provider electronically for approval. Other documentation relevant to the patient's clinical condition was recorded in the electronic health record for the provider to review. While the protocols provide a step by step approach to medication intensification, the CDEs utilized a patient-centered approach that considered the patient's attitude and expected treatment efforts, personalized goals, disease duration, support systems (including resources), risk for hypoglycemia or other adverse events, life expectancy and any comorbidities. If a medication change was ordered, CDEs followed up with the patient by phone or in person to see if any adjustment was needed. Though only four research visits were scheduled for each participant, they were encouraged to contact the CDE between visits either over the phone, via e-mail, or schedule an in person visit. All communication between the CDE and the participant, lab orders, and medication changes were recorded in the electronic medical record.

Participants randomized to the control group continued to receive standard diabetes care from their primary care providers. These participants were also offered a monthly patient-centered support group that was held at their primary care practice for the duration of the study. This support group was facilitated by one of the study's CDEs.

Regardless of randomization assignment, all participants completed surveys related to the study at each research visit. These surveys collected information pertaining to demographics, medical history, quality of life, diabetes distress, self-care activities, health care utilization, treatment satisfaction, medication adherence, cognitive status, and depression.

6.2.5 Measurements

Table 6-1 REMEDIES4D timeline and measurements relative to aims 1-3

	Assessment Timepoint (month)				
<i>Assessment Instruments</i>	<i>Baseline</i>	<i>3</i>	<i>6</i>	<i>12</i>	<i>Data Source</i>
Clinical outcome and process outcome measures	X	X	X	X	Medical Record
Sociodemographic Characteristics <i>This instrument was developed by the investigators for the REMEDIES4D study.</i>	X				Survey
Medication Satisfaction Questionnaire <i>Based off of validated questionnaires, this instrument was developed by the investigators for the REMEDIES4D study.</i>	X	X	X	X	Survey
AHRQ-CAHPS* Clinician & Group Survey: Diabetes Clinic Satisfaction Survey (244) <i>A subset of the validated AHRQ-CAHPS survey focusing on diabetes clinic satisfaction was used in REMEDIES4D.</i>	X	X	X	X	Survey
Morisky Medication Adherence Scale (MMAS)(245) <i>Used to assess patient adherence to medication, this measurement has been repeatedly validated in different populations with different medications.</i>	X	X	X	X	Survey

Table 6 1 (Continued)

Patient Health Questionnaire-9 (PHQ-9)(246) <i>A brief, validated survey that assesses the severity of depression. This instrument has 88% specificity and 88% sensitivity for detecting major depression.</i>	X	X	X	X	Survey
Montreal Cognitive Assessment (MoCA)(247; 248) <i>An interview tool used to assess mild cognitive impairment(MCI) . Among older adults, using a cut off score of 23 the MoCA has 96% sensitivity and 95% specificity in detecting MCI.</i>	X			X	Interview
Digit Symbol Substitution Test (DSST)(249) <i>The DSST measures attention, psychomotor speed, and executive function. This test is sensitive but not specific to brain dysfunction.</i>	X			X	Interview
Participant medication alterations	X	X	X	X	Medical Record

* Agency for Healthcare Research and Quality-Consumer Assessment of Healthcare Providers and Systems.

6.3 SAMPLE SIZE

The sample size estimates for this study incorporated the multilevel cluster design of the study and were performed using PASS 10.0. Estimation was based on being able to detect a mean difference of 1% HbA1c, 20 mg/dl of LDLc, and 5 mm/Hg of systolic blood pressure between the two study groups. The sample size was calculated using a two sided alpha of 0.05 and a beta of 0.2. Additionally, four parameters were used 1) the number of clusters (practices)

per group, 2) difference between group mean levels, 3) the intraclass correlation coefficient (ICC), and 4) the standard deviation. In human studies, the ICC values tend to be between 0.01 and 0.02(253). In this study, an ICC of 0.02 was used, which yielded a sample size of eight clusters per group with 11 participants per practice or 88 participants per study group. The number was sufficient to achieve at least 80% power to detect a significant difference between the primary outcomes of HbA1c, SBP, and LDLc. Additionally even though it was unlikely, a dropout rate of 25% per practice was accounted for in the calculations, bringing the total sample size up to 240 people, 120 in each arm.

Since the final enrollment was 175 in the intervention group and 65 in the control, post enrollment power calculations were performed. While the study was powered to detect a difference in HbA1C values, it was no longer powered to detect differences in blood pressure and LDLc.

6.4 STATISTICAL ANALYSES

Descriptive analyses for participant characteristics and outcomes were performed before evaluating any of the hypotheses. Evaluating variables' characteristics such as distribution, mean, and range is necessary to determine the most appropriate statistical test. Additionally, measures of central tendency, like standard deviations or proportions, were also used for any descriptive analyses. All estimates of significance used $p \leq 0.05$. All analyses were carried out using the SAS statistical software system, version 8.3, SAS Institute Inc., Cary, NC.

Specific Aim 1

a) Determine if those who received care using the REMEDIES4D protocol had improved clinical outcomes (A1C, blood pressure and LDLc) compared to those in usual care.

b) Assess differences in treatment intensification of those in the REMEDIES4D protocol group compared to those in usual care.

The primary outcomes were changes in HbA1c, blood pressure, and LDLc levels at the end of the intervention period. Treatment intensification of glucose, blood pressure, and lipid control were assessed. Medication was considered intensified if a new medication is started or if the dose of a current medication increases. Laboratory results and medication changes were retrieved via the participant's electronic health records. Clinical and medication data was collected at baseline, 3 months, 6 months, and 12 months. Baseline values could be taken up to one year in advance of the baseline visit. There was a one month window either before or after the 3, 6, and 12 month visit when clinical values could be retrieved. Medication data was collected from the research visit with the CDE or the nearest medical record that contains medication data.

Descriptive statistics, including distributions, frequencies, and means, were performed on all outcome measurements. Two sampled t-tests for continuous measures, chi-square tests for categorical variables, McNemar's test for dependent proportions, and Fisher's exact tests were used to assess the differences in baseline characteristics, including the clinical values, between the two groups. The percentage of people with clinical measurements controlled to clinical goal levels at each visit, the percentage of participants on Angiotensin Converting Enzyme Inhibitors (ACE) /Angiotensin Receptor Blocker (ARB) and statins, the proportion of participants that had their medication intensified if needed were also compared. Paired t-tests were used to assess the

within group change for the main outcome measurements. To evaluate whether there was a significant difference between groups at the end of the study, mixed models will be performed. Mixed models adjusted for the correlation of patients within practice and accounted for the correlation of the repeated measurements. All covariates were analyzed in univariable mixed models and those with a p-value ≤ 0.3 were considered eligible for the final model. Backwards stepwise regression were used to create the final mixed models with covariates ≤ 0.2 kept in the model. In order to adjust for differences in HbA1c and blood pressure at baseline, these values were included in the models. Due to missing data for HbA1c and LDLc measurements, the last available HbA1c or LDLc measurements after baseline were used as the final outcome. A sensitivity analysis was conducted for those that had data available for all visits.

Specific Aim 2

- a) Determine if those who received care using the REMEDIES4D protocol experienced increased clinic and medication satisfaction.
- b) Determine if clinic and medication satisfaction impact medication adherence and clinical outcomes (A1C, blood pressure, LDLc).

The primary outcomes were clinic satisfaction and medication satisfaction for part a of specific Aim 2. For part b, the primary outcomes were medication adherence and clinical values described in the previous aim. Descriptive statistics, including distributions and frequencies were performed on all outcome measurements. McNemar's and Fisher's exact test were used to examine unadjusted between group differences and within group change for medication and clinician satisfaction. Multicollinearity was assessed by examining variance inflation factor(VIF) for the covariates used in each model. Covariates with a VIF larger than 10 were removed from the model as VIFs above 10 indicate moderate multicollinearity(254). Mixed

models were used to evaluate the associations between the independent and outcome variables. Mixed models adjusted for the correlation of patients within practice and accounted for the correlation of the repeated measurements. Candidate covariates for the multivariable model were sex, provider rating at baseline and 12 month visit, education (Post-secondary education vs. GED/high school education or less), age, the baseline outcome measure, and overall medication satisfaction at baseline and the 12 month visit (satisfied vs unsatisfied). The intervention variable (intervention vs. usual care) was forced into the multivariable model. Backwards stepwise regression was used to create the final mixed models with covariates ≤ 0.2 kept in the model.

Specific Aim 3

3a) Determine if increased cognitive scores impacts improvement in diabetes medication adherence and HbA1c values.

3b) Determine predictors of impacts improvement in diabetes medication adherence and HbA1c values and increased cognitive scores at the end of the study.

Descriptive statistics, including distributions and frequencies were performed on all outcome measurements. Spearman correlation coefficients were used to identify associations between the independent variables and covariates not already identified from the literature. These correlations were also used to investigate possible multicollinearity between covariates. Mixed models were used to evaluate the associations between the independent and outcome variables. Mixed models adjusted for the correlation of patients within practice and accounted for the correlation of the repeated measurements. All covariates were analyzed in univariable mixed models and those with a p-value ≤ 0.1 were considered eligible for the final model. Backwards stepwise regression was used to create the final mixed models with covariates ≤ 0.05 kept in the model. All cognitive outcomes were adjusted for age and education due to strong

evidence supporting that age and education affect cognition (255; 256). Due to lack of outcome data in the control group, the analysis was limited to the intervention group.

**7.0 MANUSCRIPT 1: EFFECTIVENESS OF CERTIFIED DIABETES EDUCATORS
FOLLOWING PRE-APPROVED PROTOCOLS TO REDESIGN DIABETES CARE
DELIVERY IN PRIMARY CARE: RESULTS OF THE REMEDIES 4D TRIAL**

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7.1 ABSTRACT

Objective: To evaluate the changes in HbA1c, blood pressure, and LDL cholesterol (LDLc) levels in the participants from practices where certified diabetes educators (CDEs) implemented standardized protocols to intensify treatment compared with those who received usual care.

Research Design and Methods: This clustered, randomized, clinical trial was implemented in community-based primary care practices in southwestern Pennsylvania. Fifteen primary care practices and 240 of their patients were randomized to the intervention (n=175) or usual care (n=65). Participants had Type 2 diabetes and uncontrolled HbA1c, blood pressure, or LDLc. The one-year intervention included CDEs implementing standardized pre-approved protocols to intensify treatment using a patient-centered approach. Diabetes self-management education was also provided.

Results: The population was 50.8% male with a mean age of 61 years. At the end of the one-year intervention, there was a significant difference in HbA1c between the intervention and usual care groups. The HbA1c in the intervention group decreased from 8.8% to 7.8%, (p=0.001) while the HbA1c in the usual care group increased slightly from 8.2% to 8.3% (p=0.001). At the end of the 12-month intervention period, there was a significant difference in HbA1c between the intervention and usual care group (p=0.001). There was not a significant difference between groups for LDLc or systolic blood pressure at the end of the year intervention. Those in the intervention group were more likely to have their diabetes medication intensified and were more likely to have their HbA1c (35% vs 15%), SBP (80% vs 77%) and all

three values at goal (11% vs 1.5%) compared with the usual care group. There was no difference in intensification of blood pressure and cholesterol medication.

Conclusions: Findings suggest that CDEs following standardized protocols feasible in primary care and can effectively intensify treatment and improve glycemic control.

7.2 INTRODUCTION

Approximately 29.1 million, or 9.3% of the total US population, currently have diabetes and this number is expected to rise to 48.2 million by 2050(6; 7). As the prevalence of diabetes increases, the number of complications associated with diabetes, such as cardiovascular and renal disease, will likely also increase. With 20% of health care dollars spent on treating people with diabetes, more than twice the expense of those without diabetes, the nation faces a large healthcare and financial burden (257).

The key to reducing the number of diabetes-associated complications is to control glycated hemoglobin (HbA1c), blood pressure, and low-density lipoprotein cholesterol (LDLc) (the “ABCs”) (4; 175; 176; 258). Although some improvement in control of these risk factors has been made, recent national data from 2007-2010 suggest that those with diabetes do not have their ABC levels adequately controlled, as less than 20% met all of their goals and just over 50% were on a statin for their LDLc(4).

Despite the availability of evidence-based guidelines, failure to intensify treatment in a timely manner remains a challenge. This clinical inertia is one of the reasons for suboptimal diabetes control(189). Many people remain in poor glycemic control for years before intensification of oral anti-hyperglycemic medications or the addition of insulin to their

therapeutic regimen (189). The reasons behind clinical inertia are complex and exist at the patient, provider, and system levels, and include reasons such as time constraints, lack of provider knowledge, or fear of hypoglycemia (259). For example, in a survey of physicians, two-thirds felt that insulin therapy would be too burdensome for patients, although they agreed that patients would benefit from earlier insulin therapy(191; 260).

More than 90% of physician visits by people with diabetes occur in primary care. (21). However, there is currently a shortage of primary care providers(21), putting more constraints on an already overextended system, which could, in turn, impact quality of care. In response, the Affordable Care Act attempted to strengthen primary care through incentives for achieving certain quality of care measures (21; 238). In order to further support primary care, the Institute of Medicine recommended redesign strategies comparing the effectiveness of allied health providers for chronic conditions as a Health Care System Priority Topic(261; 262). However, there is a gap in the evidence addressing the effectiveness of this approach.

Evidence supports better quality of life and clinical outcomes can be achieved in those with chronic disease when allied health care providers make medication changes independent of the physician (215; 218; 220; 221; 224; 225). However, there is a gap in the literature examining the roles of these providers in primary care, in particular, Certified Diabetes Educators (CDEs). The present study, REdesigning MEDication Intensification Effectiveness Study for Diabetes (REMEDIES4D), was a clustered randomized clinical trial that addressed this gap using evidence-based diabetes management protocols to deploy a systematic and effective redesign of current diabetes treatment approaches in primary care. This intervention was implemented by CDEs. The objective of this study was to assess the differences in HbA1c, blood pressure, and LDLc levels in the participants where the CDE implemented the REMEDIES 4D protocols

compared with those who received usual care. We hypothesized that those randomized to the REMEDIES 4D intervention would have significant improvements in their HbA1c, LDLc, and blood pressure compared to those randomized to usual care.

7.3 MATERIALS AND METHODS

The materials and methods for this clustered randomized clinical trial have been detailed in a previous publication and will only be briefly discussed.(263)

Participants

In January 2012, 33 primary care practices from the University of Pittsburgh Medical Center (UPMC) were contacted to participate in the study. Practices had to have at least 50 patients with diabetes to be eligible. Fifteen practices agreed to participate. All providers from the practices consented to participate and were randomly assigned to the REMEDIES 4D intervention or to usual care (Figure 1). Between July 2012 and January 2014, participants were screened and consented for the study (Figure 1). Participants were recruited if they were at least 18 years of age or older; had a diagnosis of type 2 diabetes for at least one year prior to baseline; had at least one of their most recent clinical values for HbA1c ($\geq 7\%$ / 53 mmol/mol), blood pressure (SBP \geq 140 mm/Hg or DBP \geq 80 mm/Hg), or LDLc (\geq 100 mg/dL) above goal; and had at least one visit to their primary care practice within the last 12 months. Patients who were not ambulatory, had gestational diabetes, were pregnant or planning on becoming pregnant in the next year, were moderately or severely cognitively impaired, had a scheduled surgery, were on dialysis, or were not able to read or comprehend English were excluded from the study. Participants were screened over the phone to confirm eligibility and if eligible were invited to

their primary care practice for a visit with the CDE. The University of Pittsburgh IRB approved this study and Data and Safety Monitoring Board (DSMB) meetings were held quarterly throughout the study. Relevant data were reviewed at the quarterly for DSMB meetings to ensure participant safety.

Intervention

Participants from intervention practices visited the CDE for one-on-one visits at baseline, 3, 6, and 12 months. The baseline visit lasted approximately 2 hours while follow up visits ranged from 30 to 60 minutes. Treatment for glucose, blood pressure, and LDLc were reviewed and changed if necessary, according to REMEDIES 4D protocols published elsewhere (263; 264). The REMEDIES 4D protocols were derived from the evidence-based guidelines available at the start of the study in 2012. These included the ADA Standards of Medical Care(239), Standards for Diabetes Self-Management Education and Training(242), American Association of Clinical Endocrinologists Guidelines(243), National Cholesterol Educational Program Adult Treatment Plan III(244), and Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure 7 and 8(245; 246). The protocols were updated throughout the trial as evidence changed.

During the visit with the CDE, treatment and clinical parameters were reviewed and gaps in care, such as eye exams or lab tests, were addressed by the CDE and subsequently ordered. If medication changes were made, orders were marked as “pending” in the electronic health record (EHR) for provider approval and electronic transmission to the pharmacy. For medication changes, the CDEs used a patient-centered approach that considered the patient’s lifestyle, support systems, willingness to make changes, risk for hypoglycemia and other adverse events, disease duration, and established comorbidities and complications. If any medications were

started or intensified, the CDE followed up with the participant in person, via phone call, or e-mail. Also, Participants were encouraged to contact the CDE as needed. For example, patients contacted the CDE if a prescribed medication was not covered by their insurance or if they experienced any side effects after starting a new medication. All communication, lab orders, and medication adjustments were documented in the EHR. Participants from the intervention practices were paid \$50.00 at each of the four study visits in order to offset any potential increase in medical or medication expenses. Since therapeutic interventions were individualized, doses could be adjusted according to the protocols between research visits. For example, if a participant was started on insulin at a research visit, they were closely monitored as needed, by phone or in person, by the CDE for possible dosing adjustments.

Participants from control practices continued to receive usual care delivered by their providers. In addition, they were invited to attend monthly support groups held at their primary care practice for the duration of the study. These monthly support groups were patient-centered, focusing on topics of interest to the participants. These support groups were facilitated by a CDE.

Participants in both usual care and intervention groups completed surveys collecting demographic information, medical history, medication use, self-care activities(265), diabetes distress(266), treatment satisfaction, medication adherence(248), cognitive status(250; 252). The PHQ-9 was used to screen for patient depression(249). Scores <5 were categorized as minimal depression; 5-9 as mild; 10-14 as moderate; 15-19 as moderately severe; and 20-27 as severe depression.

Outcome Measurements

The primary outcomes were changes in HbA1c, blood pressure, and LDLc levels at the end of the one-year intervention period. Medication intensification for glucose, blood pressure, and lipid control was also assessed. Medication intensification is defined as the start of a new medication or if the dose of a current medication was increased. The laboratory results and medication changes were extracted from the participant's EHR. Clinical and medication data were collected at baseline, 3 months, 6 months, and 12 months. Baseline data was defined as up to one year in advance of the baseline visit. There was a one-month window either before or after the 3, 6, and 12-month visit when measurements could be retrieved. Medication data were collected from the research visit with the CDE or the nearest available visit record that contained medication data.

Statistical Analyses

Descriptive statistics, including distributions, frequencies, and means, were performed on all outcome measurements. Two sampled t-tests for continuous, chi-square tests or Fisher's exact tests, as appropriate, for categorical variables, and McNemar's test for dependent proportions, were used to assess the differences in baseline characteristics, including the ABCs, between the two groups. The percentage of people with clinical measurements controlled to clinical goal levels at each visit, the percentage of participants on ACE/ARBs and statins, the proportion of participants that had their medication intensified if needed were also compared. Medication intensification was stratified by two groups: HbA1c >7%/53 mmol/mol but ≤8%/64 mmol/mol and >8%/64 mmol/mol. This was done to examine what proportion of participants who had room for improvement but were not considered out of control (HbA1c >7%/53 mmol/mol but ≤8%/64 mmol/mol) had a medication change and what proportion of patients who had

uncontrolled HbA1c ($>8\%/64$ mmol/mol) had a medication change. Paired t-tests were used to assess the within-group change for the main outcome measurements. To evaluate whether there was a significant difference between groups at the end of the study, mixed models were used (Proc Mixed). Mixed models adjusted for the correlation of patients within practice and accounted for the correlation of the repeated measurements. All covariates were analyzed in univariable mixed models and those with a p-value ≤ 0.3 were considered eligible for the final model. Backwards stepwise regression was used to create the final mixed models, with covariates ≤ 0.2 kept in the model. In order to adjust for differences in HbA1c and blood pressure at baseline, these values were forced in the models. Due to missing data for HbA1c and LDLc measurements, the last available HbA1c or LDLc measurements after baseline were used as the final outcome. The LDLc, SBP, and DBP distributions were squared to account for their skewed distribution. A sensitivity analysis was conducted for those that had data available for all visits. The *a priori* sample size calculations for the trial showed that with an intraclass correlation coefficient of 0.2 we had at least 80% power to detect differences of 1% in HbA1c, 20 mg/dl in LDLc, and 5 mmHg in SBP (263) with 120 people in each of the two arms. All analyses were carried out using the SAS statistical software system, version 8.3, SAS Institute Inc., Cary, NC.

7.4 RESULTS

Characteristics of the participants by group are detailed in Table 7-1. Intervention participants were significantly less likely to be white ($p=0.03$) and significantly more likely to have lower blood pressure as compared with the control group (SBP: 129.1 vs 133.6, $p=0.03$; DBP: 76.8 vs 79.6, $p=0.01$). Intervention participants were significantly more likely to have

higher HbA1c compared with those in the usual care group (8.8%/ 73 mmol/mol vs 8.2%/ 66 mmol/mol, $p=0.007$). There was not a significant difference in LDLc between the groups. Intervention participants were more likely to have moderately severe depression according to their PHQ-9 scores while participants in the usual care group were more likely to have scores in the severe category of depression.

Over the course of the study, those in the intervention group had a statistically significant improvement in HbA1c from baseline while the control group's HbA1c stayed stable (Figure 7-2A). The greatest change in HbA1c in the intervention group occurred at the 3 month visit, when the mean HbA1c dropped 1.1% (13 mmol/mol). Participants in the usual care group had a non-significant decrease (0.3%/ 3.3 mmol/mol) in HbA1c levels at 3 months. Participants in both the intervention group and the usual care group had significant decreases in their average LDLc (Figure 7-2B) (104.9 mg/dl vs 88.7 mg/dl; $p < 0.0001$) (99.6 mg/dl vs 90.3 mg/dl; $p=0.039$) respectively. The control group participants had a significant reduction in their diastolic blood pressure (79.7 mmHg vs 76.5 mmHg; $p = 0.008$) but not in systolic blood pressure (Figure 7-2C and D). There was no significant change in blood pressure values in the intervention group between baseline and the 12-month visit.

At the end of the study, there was a significant difference in HbA1c between the intervention and control groups (Table 7-2). After adjusting for baseline HbA1c, income, and sex, those in the intervention group had an HbA1c that was 0.73 (95% CI: 0.29, 1.17) lower than those in the usual care. There was not a significant difference between the two groups for LDLc or SBP. The usual care group did have significantly lower DBP compared to the intervention group after adjusting for baseline DBP and SBP at the end of the study.

Participants in the intervention group were more likely to have their diabetes medication intensified throughout the study. There were significant differences between groups in the proportion of participants that had their diabetes medication intensified during the intervention period (Figure 7-3). When analysis was restricted only to participants who had an $\text{HbA1c} > 7\%/53 \text{ mmol/mol}$ but $\leq 8\%/64 \text{ mmol/mol}$, there were significant differences between the baseline and the 3-month visit (Figure 7-3A). When restricted to participants that had $\text{HbA1c} > 8\%/64 \text{ mmol/mol}$ (Figure 7-3B), significant differences were observed between groups at the baseline, 3, and 6 month visits. In those with a $\text{HbA1c} > 8\%/64 \text{ mmol/mol}$ in the intervention group, 43% either started insulin therapy or had another insulin, such as meal time, added to their regimen. In the same group, 90% of participants' insulin dosage was increased. There was not a significant difference in intensification of blood pressure (Figure 7-3C) or LDLc medications (Figure 7-3D) at any time. There was no significant difference between the two groups when it came to ACE/ARB or statin use. There was also not a significant change in either ACE/ARB or statin use within the groups throughout the study (Figure 7-4).

Between the two groups, there was a significant difference in the proportion of patients with HbA1c at goal levels at the 12 month follow-up and borderline significant differences at the 3- and 6-month follow-up. The intervention group had a significantly higher proportion of participants with controlled DBP at baseline and the 3-month follow-up, as well as a higher proportion of participants with controlled SBP at the 3-month visit. In the control group, there was not a significant within group change in the proportion of participants achieving their HbA1c , LDLc, SBP, or DBP goals (Figure 7-5a). In the intervention group, there was a significant increase in the proportion of participants who reached HbA1c goal when comparing baseline and the 12-month visit, as well as in increase in the proportion at the 3- and 6-month

visits (Figure 7-5b). There was also a significant increase in the proportion of intervention patients achieving LDLc goal at the 3-month visit, that held throughout the course of the study. There was a significant decrease in proportion of patients who achieved their SBP goal at the 6-month visit but this was not a significant throughout the course of the study. Lastly, there was a significant difference ($p=0.02$) in the percentage of patients who had all clinical values controlled at the end of the study (Figure 7-5).

7.5 DISCUSSION

Results of this study indicate that use of allied health care providers, specifically nurse CDEs, in primary care practices can facilitate intensification of diabetes treatment resulting in better glycemic control. A 1.0% decrease in HbA1c in the intervention group was maintained throughout the trial, showing that the gains made in glycemic control were sustainable in this model. Participants in the usual care group, on average, had significantly better control of their HbA1c ($p = 0.007$) at baseline. Even though they experienced a small, non-significant drop in HbA1c at 3 months, there was ultimately no improvement in glycemic control throughout the study. These participants were also less likely to have their medication intensified and were more likely to experience a delay in medication intensification compared to the intervention group.

There was not a significant difference between groups in LDLc levels at baseline or at the end of the study, however both groups had a significant reduction in their LDLc throughout the study, with the average LDLc decreasing from 104.9 mg/dL to 88.7 mg/dL in the intervention group and 99.7 mg/dL to 90.3 mg/dL in the control group. By the end of the study, the average

LDLc in both groups was below goal levels. There was a significant reduction in LDLc within both groups but no statistically significant difference between groups, perhaps due to existing quality improvement initiatives already in place, leaving little room for improvement.

At the end of the study, there was not a difference in the blood pressure levels between groups. The control group had significantly higher levels of SBP (133.6mmHg vs 129.1mmHg) and DBP (79.8mmHg vs 76.8mmHg) compared with the intervention group at baseline. This difference in blood pressure levels may explain why those in the control group had a significant decrease in blood pressure levels throughout the study compared with the intervention group. The intervention group already, on average, had well controlled blood pressure that met the recommended blood pressure goals. This may explain the lack of significant differences between the two groups in medication intensification.

During the course of the study, the American Diabetes Association updated their Standards of Care guidelines for diabetes treatment to reflect more individualized goals, based on the patient's overall health(239). Therefore, the treatment goals used at the beginning of the study ($\text{HbA1c} \leq 7\%$ / 53 mmol/mol, $\text{SBP} \leq 140$ mm/Hg or $\text{DBP} \leq 80$ mm/Hg, or $\text{LDLc} \leq 100$ mg/dL) could be perceived as too strict for some of the patients in the study population. Although the treatment protocols were updated throughout the course of the study to reflect the most recent evidence and to individualize the participant's care, the study's definition of what was considered "control" was not changed. The individualized nature of the protocols took into account: patient attitudes and expected treatment efforts; risks of adverse events, such as hypoglycemia; disease duration; life expectancy; important comorbidities; established vascular complications; resources and support systems(267). This may explain why so few participants achieved the previously defined treatment goal for all three measurements at the end of the study.

We hypothesize that the individualized nature of the care, which considered the patients' goals, and possible extant co-morbidities may have contraindicated tighter control.

Previous research has shown that patients treated by allied health care providers (including pharmacists and nurses) achieved better glycemic(215-218; 221-224), blood pressure(218; 220-222), cholesterol control(218; 221-223), emotional distress scores, and more frequent screening for diabetes complications (220). The addition of pharmacists to the primary care team significantly improved patient's HbA1c, LDLc, and blood pressure measurements, reducing their 10 year risk of coronary heart disease from 17.4% to 14.8% (221). Similarly, in an integrated model where a nurse, following pre-approved protocols, was placed in a primary care clinic, patients had a 3.9% reduction in their HbA1c(218). Care teams that integrate allied health care providers consistently demonstrate their ability to effectively and safely improve patients' clinical outcomes (216; 217; 224; 225). While integrating allied health care providers may not always lead to significantly better clinical outcomes, such as in the DREAM 3 trial where both the nurse centered group and the primary care provider control group experienced reductions in blood pressure but not a statistically significant difference, there has not been evidence to suggest that their care is substandard relative to the usual care a patient may receive from a physician(226). The utilization of allied health care providers in primary care may therefore be a mechanism to overcome clinical inertia(222), support primary care providers, and potentially reduce costs.

The REMEDIES 4D model used allied health care providers (CDEs), following pre-approved standardized treatment protocols, to intensify treatment. This model was successfully integrated into existing primary care practices (218; 225; 226). REMEDIES 4D is the first broad scale randomized clinical trial where allied health care providers went into a large number of

stand-alone primary care practices and intensified treatment using pre-approved protocols. While all practices were part of the UPMC health care system, the practices accepted a variety of insurances and were not academically affiliated. This increased the generalizability of our model to other primary care settings. The CDEs, while collaborative, were independent of the provider and followed a standardized protocol to intensify treatment. Since the primary care providers still had to approve the medication changes that the CDE ordered through the EHR, the primary care provider was able to monitor all medication changes.

This study had some limitations that must be addressed. There was a significant difference in HbA1c measurements at baseline between the groups. This could be due to intervention providers encouraging their sicker patients to participate in the REMEDIES 4D study and could contribute to the differences in the decreases in HbA1c between the two groups. To address this limitation, baseline HbA1c values were controlled for in the mixed models. Another limitation was missing clinical values in the EHR. In the intervention group, the CDEs had the opportunity to order cholesterol and HbA1c tests for the participants, in addition to taking the participants' blood pressure at clinical visits. However, in the usual care group, if their primary care provider did not order cholesterol or HbA1c tests, the researchers had no mechanism to order tests, which led to the missing data. Also, the CDE leading the support groups for the usual care group did not take the participants' blood pressure, so if the participant did not have an eligible visit with a blood pressure reading recorded in the EHR, this was a missing data point. Despite this limitation, we feel that the data collected in the usual care group was a true reflection of usual primary care. While the CDEs ordered the labs in the intervention group, participants may not actually follow through and have the lab work completed. Again, this is more reflective of processes in primary care. Due to the design of the study, the blood

pressure measurements were not consistently taken by the same person and may have introduced variability into the measure, however the blood pressure measurements were not intended to follow a strict research measurement protocol, but rather the standard of good clinical practice. Finally, this study originally aimed to have 120 participants in each arm in order to be powered to detect differences in HbA1c, blood pressure and LDLc. This accounted for an anticipated 25% drop-out rate(263). The recruitment goal was not reached in the usual care group. Post-enrollment power calculations showed that while this study was still powered to detect differences in HbA1c, it was not powered to detect differences in blood pressure and LDLc. Despite the average value for the clinical measures being at goal levels in both groups, the study may have suffered from Type II error. Over 80% of the population in this study was non-Hispanic white. This precluded the ability to do subgroup analyses based on race or ethnicity, therefore this study may not be generalizable to other ethnic and racial groups. Some of these limitations can be addressed in future research, in larger, more diverse populations, to examine the effectiveness of this approach in different ethnic and racial groups. Future studies should also examine the cost-effectiveness of CDEs in the primary care setting.

In conclusion, this study supports that a CDE in a primary care practice can facilitate the achievement of therapeutic goals. Better control of HbA1c, LDLc, and blood pressure reduces the risk of diabetes complications, and could potentially save billions of dollars in healthcare expenditures (4; 175; 268). Diabetes is a major health care concern in the United States and around the world. With the shortage of primary care physicians, the approach used in REMEDIES 4D has the potential to reduce the current and future clinical and financial burden of diabetes and potentially its complications.

7.6 TABLES AND TABLE LEGENDS

Table 7-1 REMEDIES4D timeline. Baseline Characteristics of REMEDIES 4D Population by study group

	Intervention		Usual Care		
	(n)	Mean (SD) or %	(n)	Mean (SD) or %	P-value
Age (years)	175	60.3 (10.2)	65	61.8 (10.8)	0.38
Gender					
Female	88	50.3	30	46.2	0.41
Male	87	49.7	35	53.8	
Race					
White	137	79.6	59	93.6	0.03
Black	29	16.8	4	6.3	
Other	4	2.3	0	0	
Diabetes duration (years)	170	12.2 (8.6)	63	10.7 (7.3)	0.17
Education					
High school/GED or less	64	37.6	21	33.3	0.54
College/technical school or higher	106	62.3	42	66.6	
Missing	5	2.9	2	3.1	
Smoking					
Never Smoke	76	44.7	35	58.3	0.16
Former Smoker	71	41.7	23	38.3	
Smoker	23	13.5	5	8.3	
Employment					
Employed	76	43.4	27	41.5	0.84
Unemployed	41	23.4	13	20.0	
Retired	49	28.0	20	30.8	
Missing	6	3.4	3	4.6	
Other	3	1.7	2	3.1	
Annual income					
Less than \$30,000	62	36.5	15	23.1	0.15
\$30,000 or higher	103	58.8	39	60.0	
Missing	5	4.5	9	16.9	
Health insurance *					
Private insurance	114	66.2	38	60.3	0.39

Table 7-1 (Continued)

Medicaid	14	8.1	5	7.9	0.95
Medicare ± Medicare Supplement	61	35.4	25	39.6	0.55
Other	9	5.2	4	6.3	0.74
No insurance	3	1.7	0	0%	0.56
Missing	3	1.7	3	4.6%	
HbA1c (%)/mmol/mol	175	8.8 (1.7)/ 73 (18.6)	63	8.2 (1.4)/ 66 (15.3)	0.007
Systolic blood pressure (mmHg)	175	129.1 (14.5)	63	133.6 (13.7)	0.03
Diastolic blood pressure (mmHg)	175	76.8 (7.8)	63	79.6 (9.3)	0.018
LDL cholesterol (mg/dL)	172	105.0 (40.0)	58	99.6 (35.2)	0.37
Hypertension					
Yes	122	71.7	43	68.2	0.69
Hyperlipidemia					
Yes	128	75.2	44	69.8	0.54
Microvascular complications[†]					
Yes	100	59.5	41	65.0	0.44
Macrovascular complications[‡]					
Yes	76	44.9	29	46.0	0.88
Depression severity[§]					(overall : 0.007)
None/minimal	68	39.5	32	50.0	0.15
Mild	49	28.4	18	28.1	0.94
Moderate	34	19.7	9	14.0	0.30
Moderately severe	20	11.6	1	1.5	0.01
Severe	1	0.5	4	6.2	0.02
Missing	3	1.7	0	0	

Continuous variables are displayed as mean (SD) and categorical variables are displayed as percentage.

Abbreviations: GED, general educational development; LDL, low-density lipoprotein.

* Patients may have more than one insurance plan.

† Microvascular complications included retinopathy, neuropathy, or nephropathy.

‡ Macrovascular complications included coronary heart disease, cerebrovascular disease, or peripheral vascular disease.

§ Depression severity was defined by PHQ-9 score: none/minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27).

Table 7-2 Univariable models and multivariable models for clinical outcomes in REMEDIES 4D

Outcome	Univariable Results (95% CI)	p-value	Multivariable Results (95% CI)	p-value
HbA1c * Last Available	-0.47 (-0.03, -0.94)	0.04	-0.73 (-0.29, -1.17)	0.001
SBP† at Visit 4	- 0.08 (-0.28, 0.122)	0.46	-0.01 (-0.21, 0.19)	0.99
DBP‡ at Visit 4	0.08 (-0.22, 0.165)	0.39	0.15 (0.02, 0.30)	0.029
LDL § Last Available	1.75 (-0.544, 2.46)	0.99	-0.09 (-0.52, 0.343)	0.68

While other factors were tested, only those with a p-value ≤ 0.2 were retained

*Adjusted for baseline HbA1c, income, sex

†Adjusted for baseline SBP, income, hyperlipidemia status

‡ Adjusted for baseline DBP and SBP

§Adjusted for baseline LDL and hyperlipidemia status

7.7 FIGURES

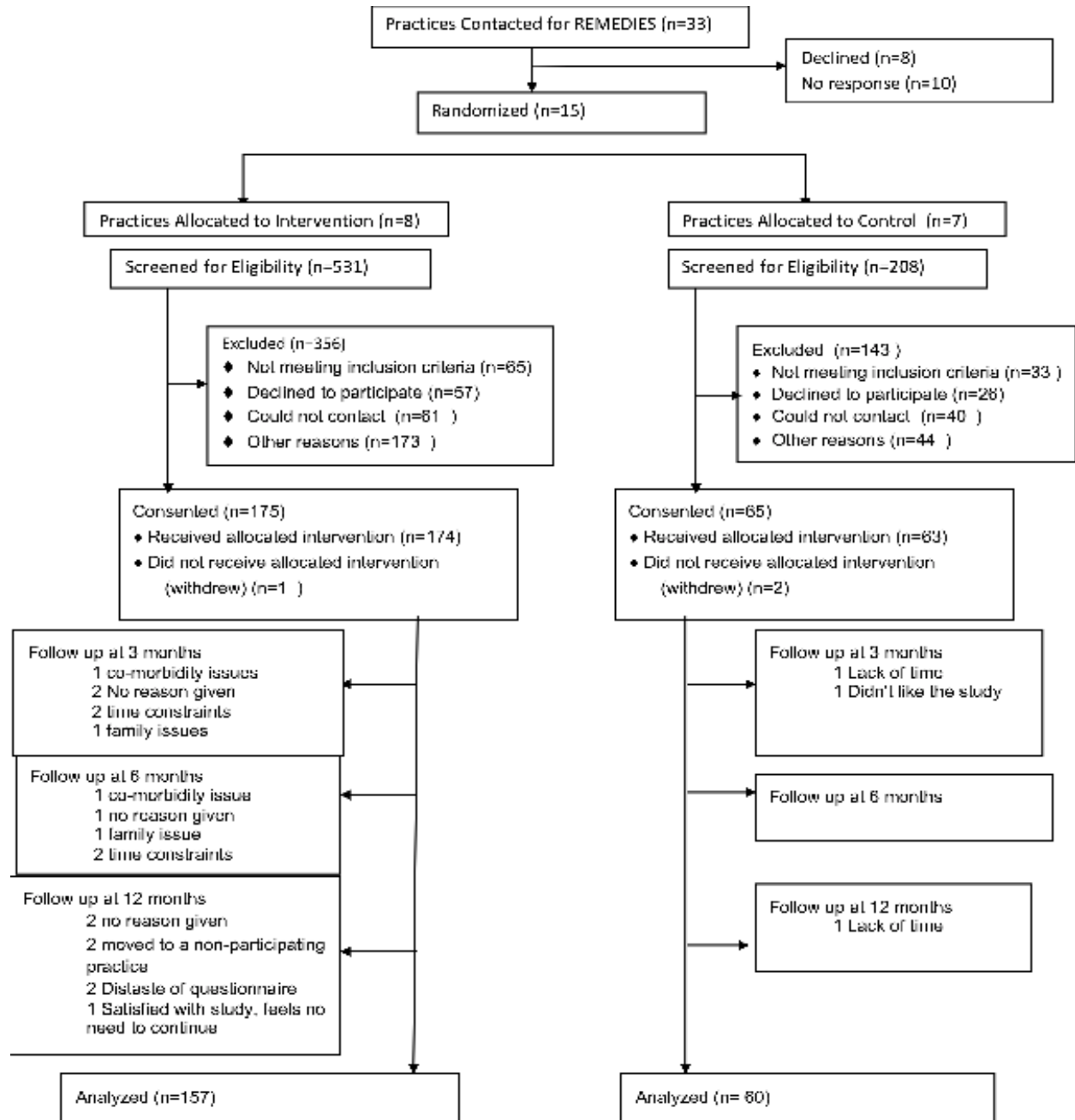


Figure 7-1 Consort diagram for the REMEDIES 4D trial

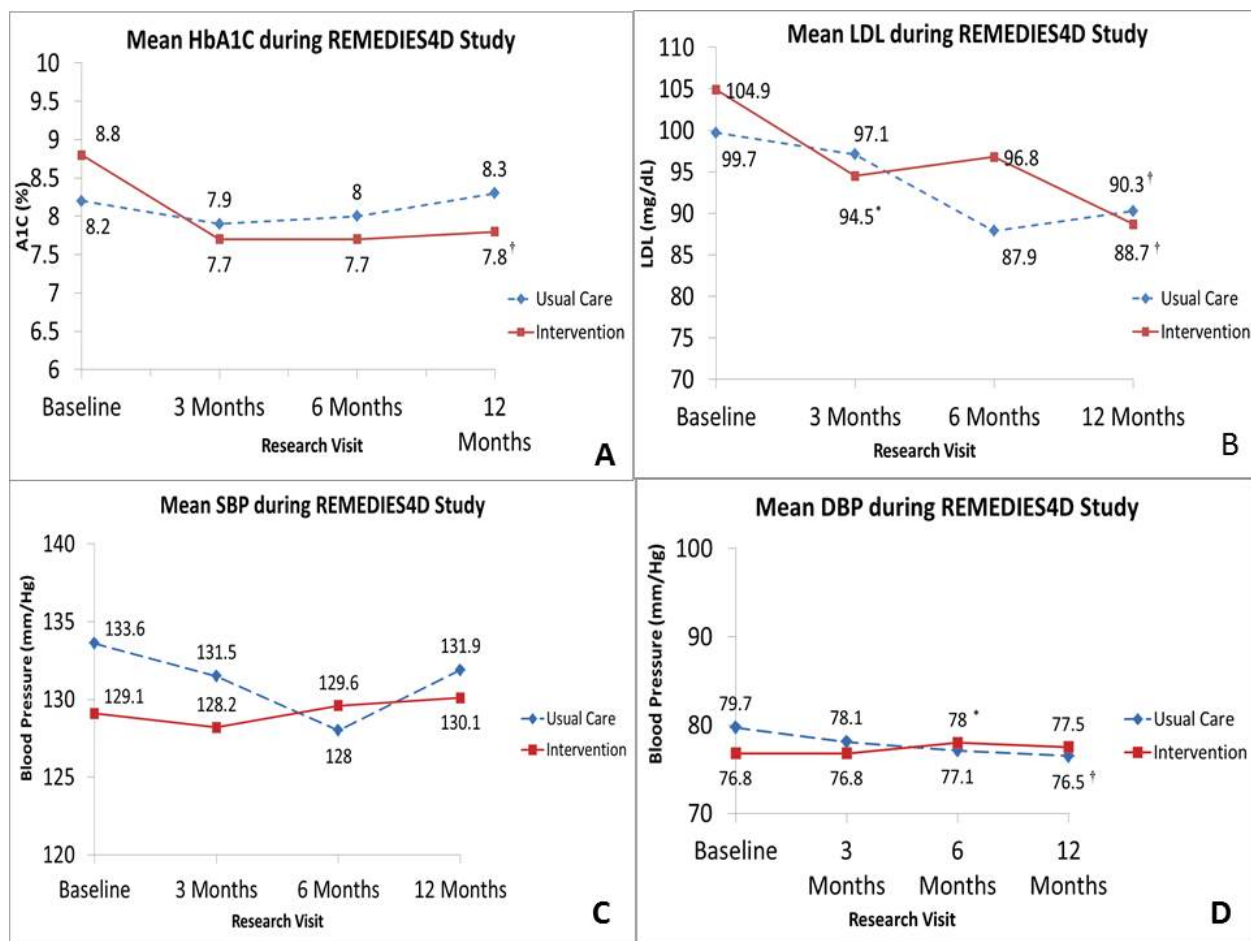


Figure 7-2 Mean change in HbA1c, blood pressure, and LDLc during the REMEDIES4D study

* Significant change from previous visit

† Significant change between baseline and 12 month visit

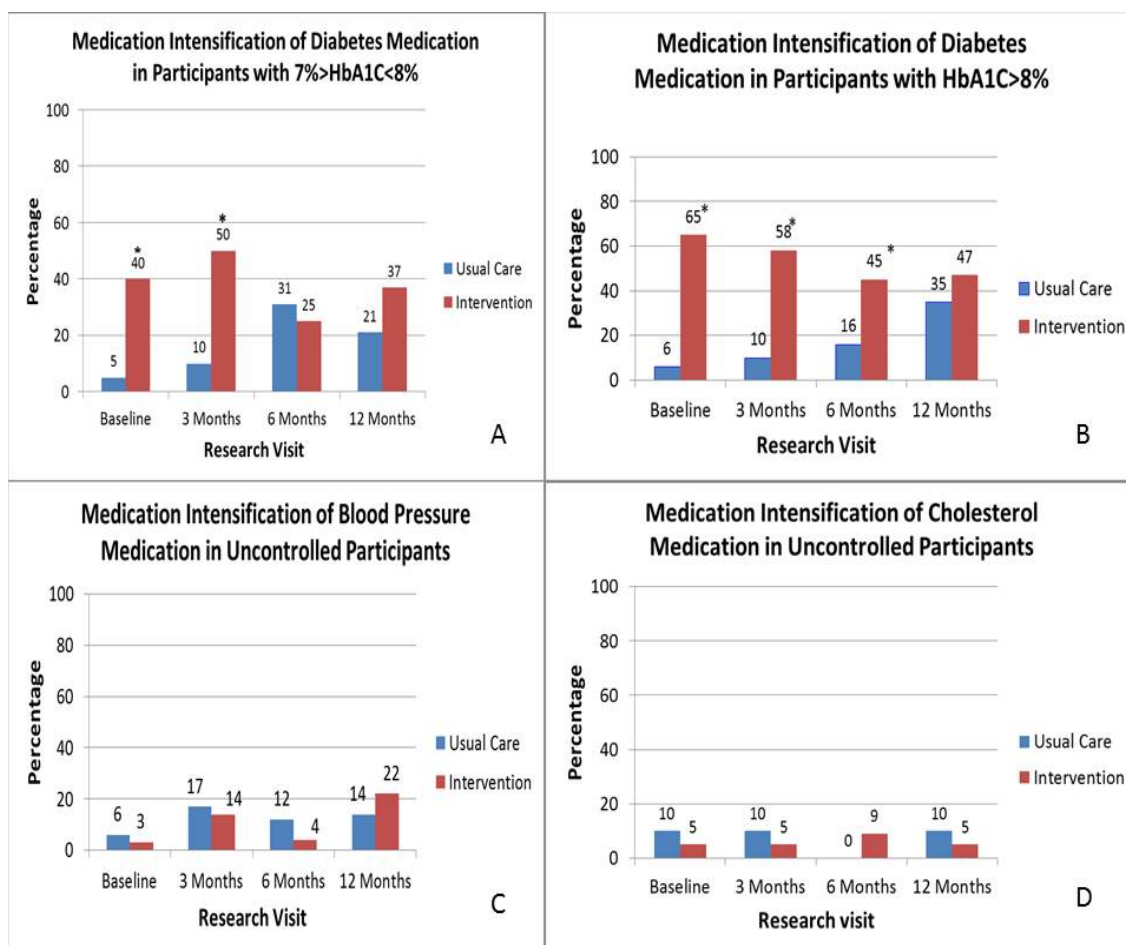


Figure 7-3 Percentage of participants who did not meet goal at baseline who had medication intensified through the REMEDIES 4D study by visit

* Significant difference between groups

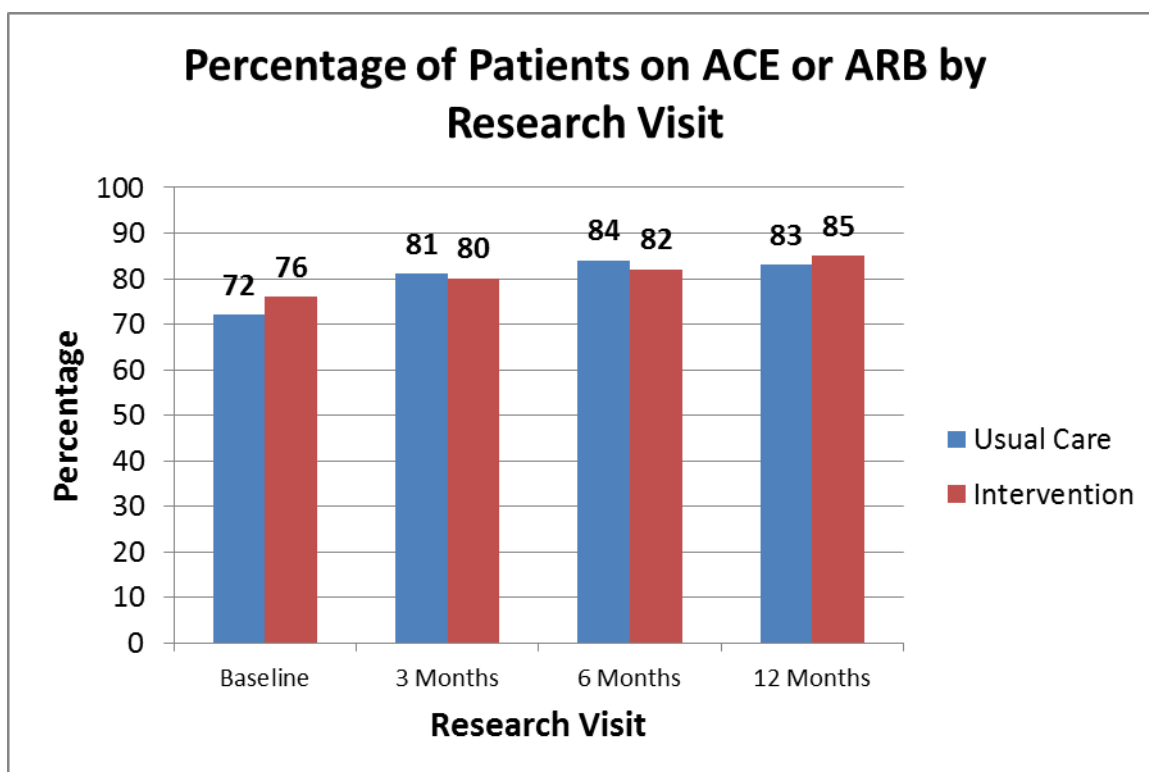


Figure 7-4 Percentage of patients on ACE or ARB by research visit

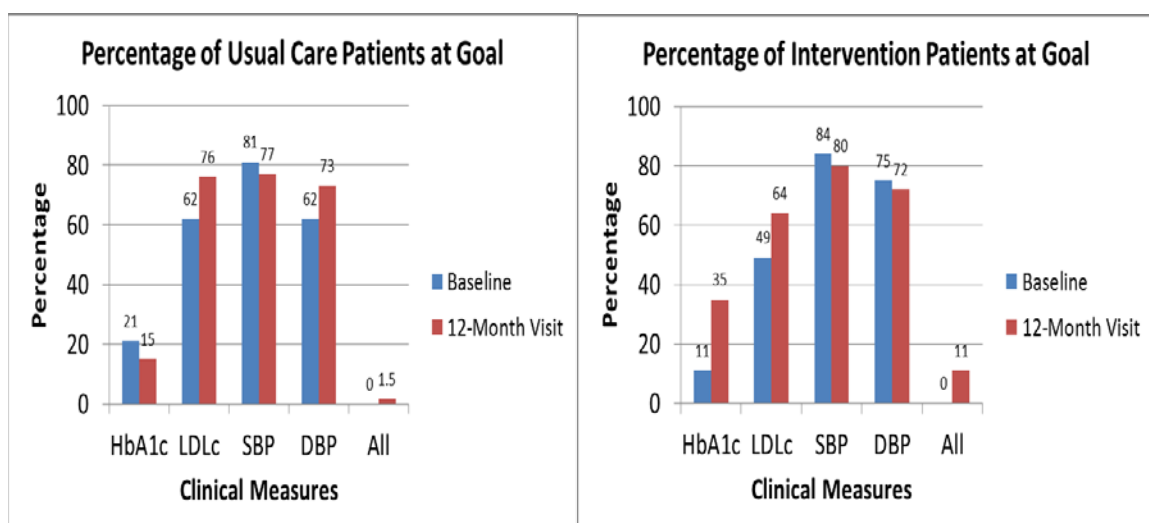


Figure 7-5 Proportion of patients at goal at each research visit by randomized group

**8.0 MANUSCRIPT 2: CLINICIAN AND MEDICATION SATISFACTION AND
THEIR IMPACT ON CLINICAL OUTCOMES AND MEDICATION ADHERENCE**

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8.1 ABSTRACT

Objective: The objective of this analysis was first to, to determine if the intervention led to improved satisfaction regarding medications and clinicians. A second objective was to see if medication and clinician satisfaction led to improved medication adherence and clinical outcomes.

Research Design and Methods: This clustered, randomized, clinical trial was implemented in community-based primary care practices in southwestern Pennsylvania. Fifteen primary care practices and 240 of their patients were randomized to the intervention (n=175) or usual care (n=65). Participants had Type 2 diabetes and uncontrolled HbA1c, blood pressure, or LDLc. The primary outcomes were the continuous variables: HbA1c, blood pressure, and LDLc levels, as well as the MMAS-8 (continuous) for diabetes, hypertension, and hyperlipidemia medications at the end of the one-year intervention period. Clinical data were collected at baseline, then at 3-, 6-, and 12-month follow-ups.

Results: Higher rating of the provider at baseline, being in the intervention group, and having higher age significantly reduced HbA1c. Baseline satisfaction of all medication, feeling their provider gives easy-to-understand answers to health care issues at 12 months, and that their provider is respectful at baseline, was decreased in SBP. Better DBP at the end of the study was associated with baseline feelings of satisfaction with hypertension medication side effects and how well a provider gives easy-to-understand answers to health care issues at the end of the study. How respectful a patient felt a provider was at baseline, how satisfied a participant is that their provider gives easy-to-understand answers to health care issues at the end of the study,

baseline feelings that hyperlipidemia medication was working, and that being satisfied with the side effects of their hyperlipidemia medication at baseline reduced LDLc. Participants who rated their provider highly during the baseline visit had better adherence to their diabetes medication at the end of the study compared with those who did not. For blood pressure medication adherence, patients who reported at the 12-month visit that their providers had enough time had worse adherence to blood pressure. Those who had higher baseline anti-hyperlipidemia medication adherence and felt their provider was respectful at the end of the study had have higher adherence.

Conclusions: The results of this analysis identified how provider and medication satisfaction scores could affect medication adherence and clinical outcomes.

8.2 INTRODUCTION

Diabetes is a known public health concern in the United States as an estimated 9.3% of the adult population has the disease, a percentage that is expected to rise dramatically in the next few decades(6; 7). With the projected increase in the number of people living with diabetes, the number of complications related to the disease will likely increase as well. There are numerous micro- and macrovascular complications associated with hyperglycemia. These complications impact a person's quality of life and can lead to premature death(7). Additionally, complications from diabetes are a large financial burden, with 20% of health care dollars spent treating those with diabetes, more than twice that spent on treating those without the disease(257).

Studies show that the key to reducing the number of diabetes-associated complications is to control glycated hemoglobin (HbA1c), blood pressure, and low-density lipoprotein cholesterol

(LDLc) (the “ABCs”) (4; 175; 176; 258). Previous large clinical trials such as United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that a reduction of 1% of glycated hemoglobin (HbA1c) resulted in a 35% reduction in microvascular complications in those with type 2 diabetes, a 25% reduction in diabetes-related deaths, and an 18% reduction in myocardial infarctions (175; 269).

One of the major factors to maintaining good glycemic, blood pressure, and cholesterol levels is adherence to a prescribed drug regimen. Those who are more adherent to their medications have lower HbA1c values compared with those who were less adherent (270). Similarly, patients with diabetes who adhere to their statin therapies are more likely to attain their LDLc goal than those who do not (271). The same pattern is seen in people with diabetes who also have hypertension; those who are more adherent to their medication have better clinical outcomes compared with non-adherent patients(272).

Despite the importance of the ABC goals and adherence, it is estimated that less than 20% of those with diabetes have their levels adequately controlled and one-third to one-half of those with diabetes are considered non-adherent(4; 273). However, if patients are satisfied with their healthcare provider or feel they have a good relationship with their physician, they are more likely have higher adherence to their diabetes regimen, whereas patients who believe their provider is a poor communicator are more likely to be less adherent(200; 274; 275). Additionally, the provider’s ability to communicate with the patient is important to ensure that the patient understands their health issues and their therapeutic regimen(276).

Another barrier to proper adherence is how satisfied patients are with their medications. Patients who are not satisfied with their medication, including but not limited to dissatisfaction in their effectiveness and convenience, are less likely to be adherent(277). Studies examining

patient satisfaction and adherence are not common but a 2012 meta-analysis showed that adherence to treatment is associated with greater treatment satisfaction and lower regimen complexity or treatment burden(278).

The REdesigning MEDication Intensification Effectiveness Study for Diabetes (REMEDIES 4D) was a 12-month patient centered (middle-aged and older adults with T2D) intervention trial in which certified diabetes educators (CDEs) provided the intervention group with diabetes education and intensified treatment using preapproved, evidence-based protocols; the control group received diabetes care as usual, with a support group run by a CDE. Compared with those in the usual care group, those in the intervention group were significantly more likely to experience a reduction in HbA1c throughout the course of the study (unpublished data). The objective of this analysis was first to, to determine if the intervention led to improved satisfaction regarding medications and clinicians. A second objective was to see if medication and clinician satisfaction led to improved medication adherence and clinical outcomes.

8.3 MATERIALS AND METHODS

The materials and methods for the REMEDIES 4D trial have been detailed in a previous publication and will only be briefly discussed (263).

Participants

The REMEDIES 4D trial was a clustered, randomized, clinical trial randomizing 15 primary care practices to either the intervention protocol or usual care. Randomization assigned eight practices to the intervention group and seven to usual care. Patients with T2D were screened over the phone and consented at the primary care practices between July 2012 and

January 2014. Eligible patients were at least 18 years of age; had a diagnosis of type 2 diabetes for at least one year prior to baseline; had at least one visit to their primary care provider within the last 12 months; and had at least one of their most recent clinical values for HbA1c ($\geq 7\%$), blood pressure (SBP ≥ 140 mm/Hg or DBP ≥ 80 mm/Hg), or LDLc (≥ 100 mg/dL) above goal. Exclusion criteria included patients who were not ambulatory, had gestational diabetes, were pregnant or planning on becoming pregnant during the course of the study, had a scheduled surgery, were on dialysis, were unable to read or comprehend English, or had a clinical diagnosis of cognitive impairment. By the end of recruitment, 175 patients were enrolled in the intervention group and 65 were enrolled in the usual care group. The study population was 50.8% male, with a mean age of 61 years, and was 81.6% non-Hispanic white.

Intervention

During the REMEDIES 4D trial, CDEs provided the intervention group with diabetes education and intensified treatment over the one year intervention period, using preapproved, evidence-based protocols. Protocols were derived from evidence-based guidelines that were available at the start of the study (2012) and were updated throughout the trial as evidence changed. Participants at the usual care practices continued to receive care delivered by their providers. In addition, they were invited to attend monthly support groups held at their primary care practice for the duration of the study. These monthly support groups were patient centered and led by a CDE. In addition to extracting clinical values and medication changes from the electronic health record (EHR) from both the intervention and usual care groups, demographic, medical history, medication use, self-care activities(265), diabetes distress(266), Morisky Medication Adherence Score (MMAS-8)(248), cognitive status(250; 252). and depression(249)information was collected via surveys. Participants also filled out the Agency for

Healthcare Research and Quality-Consumer Assessment of Healthcare Providers and Systems (AHRQ-CAHPS) Clinician & Group Survey: Diabetes Clinic Satisfaction Survey, asking them about their relationship and satisfaction with their diabetes care provider at every visit(247) (see boxed text). Participants rated their provider overall and were asked questions pertaining to more specific areas including how satisfied they were that their provider listened to them, answered their questions, respected them, or spent enough time with them during an office visit. At every research visit, participants were also asked to rate their satisfaction with their medication (see boxed text). These questions asked for overall medication satisfaction as well as satisfaction specifically relating to their diabetes, hypertension, and hyperlipidemia medications. Participants rated their satisfaction in how well their medication works, the side effects of the medication, their medication care plan, and their overall satisfaction with all of their medication.

Questionnaire	Scale	Dichotomized Scale Analysis
AHRQ-CAHPS Clinician & Group Survey: Diabetes Clinic Satisfaction Survey	Never, Sometimes, Usually, Always	Satisfied=Always Not Satisfied= Never, Sometimes, Usually
Medication Satisfaction Survey	Extremely Dissatisfied, Somewhat Dissatisfied, Neither Satisfied of Dissatisfied, Somewhat Satisfied, Extremely Satisfied	Satisfied=Extremely Satisfied Not Satisfied=Extremely Dissatisfied, Somewhat Dissatisfied, Neither Satisfied of Dissatisfied, Somewhat Satisfied

Outcome Measurements

The primary outcomes were the continuous variables: HbA1c, blood pressure, and LDLc levels, as well as the MMAS-8 (continuous) for diabetes, hypertension, and hyperlipidemia medications at the end of the one-year intervention period. Clinical data were collected at baseline, then at 3-, 6-, and 12-month follow-ups. Data relevant to the baseline visit could be extracted for up to one year in advance of the baseline visit. There was a one-month window

either before or after the 3-, 6-, and 12-month visit when measurements could be retrieved. Medication adherence was the summation of the MMAS-8 which was collected at baseline, 3-, 6-, and 12-month visits.

Statistical Analysis

Descriptive statistics, including distributions and frequencies, were performed on all outcome measurements. McNemar's and Fisher's exact test were used to examine unadjusted between-group differences, and within-group changes in medication and clinician satisfaction. Multicollinearity was assessed by examining the variance inflation factor (VIF) for the covariates used in each model. Covariates with a VIF ≥ 10 were removed from the model as VIFs ≥ 10 indicate moderate multicollinearity(254). Mixed models were used to evaluate the associations between the independent and outcome variables; these models adjusted for the correlation of patients within practices and accounted for the correlation of the repeated measurements. Candidate covariates for the multivariable model were sex; provider rating at baseline and the 12-month visit; education (post-secondary education vs. GED/high school education or less); age; the baseline outcome measure; and overall medication satisfaction at baseline and the 12-month visit (satisfied vs unsatisfied). The intervention variable (intervention vs. usual care) was forced into the multivariable model. Backwards stepwise regression was used to create the final mixed models, with covariates significant at $p \leq 0.2$ kept in the model. All analyses were carried out using the SAS statistical software system, version 8.3, SAS Institute Inc., Cary, NC.

8.4 RESULTS

The demographic information for the REMEDIES 4D cohort is reported in Table 8-1. Intervention group participants were significantly less likely to be non-Hispanic white ($p=0.03$) and significantly more likely to have lower baseline blood pressure (SBP: 129.1 vs 133.6, $p=0.03$; DBP: 76.8 vs 79.6, $p=0.01$), compared with those in usual care. Intervention group participants were significantly more likely to have higher baseline HbA1c (8.8%/ 73 mmol/mol vs 8.2%/ 66 mmol/mol, $p=0.007$) compared with those in the usual care group. There was not a significant difference in baseline LDLc between the groups.

Effect of Group Assignment on Clinical Outcomes

There was not a significant difference at baseline between the two groups in clinician or medication satisfaction with the exception that those in the intervention group were significantly less likely to be satisfied with their overall medication (Figure 8-1). There were not many significant changes within group. The proportion of those in the intervention group that were satisfied regarding how their diabetes medication worked increased and the proportion of participants in the usual care group who were satisfied overall with their medication and how well their provider listened decreased significantly from baseline to the 12-month follow up.

There were a number of statistically-significant between-group differences at the end of the study. Compared with controls, participants in the intervention group reported higher satisfaction in the following areas: provider listened to them; respected them; explained things; answered questions; felt their provider was informed about their medical history; and overall satisfaction with the provider (Figure 8-2.). Intervention group participants also reported higher satisfaction in how their diabetes medication and hypertension medication worked; side effects;

being able to plan for when to take hypertension medications; and overall satisfaction all of their medications (Figure 8-3).

Satisfaction Impact on Clinical Outcomes

Higher rating of the provider at baseline, being in the intervention group, and having higher age were significantly associated with lower HbA1c at the end of the study (Table 8-2). Having a high school education or less, a higher HbA1c at baseline, and feeling your provider had enough time for you at the end of the study were significantly associated with higher HbA1c at the end of the study. While not statistically significant, being female, feeling respected by your provider at the end of the study, feeling your provider listens to you at baseline, overall satisfaction with diabetes medication at the end of the study, and satisfaction in how diabetes medication works at 12 months also contributed to HbA1c at the end of the study.

Being satisfied with all of their medication at baseline, feeling their provider gives easy-to-understand answers to health care issues at 12 months, and that their provider is respectful at baseline, was associated with a decrease in SBP at the end of the study (Table 8-3). Being satisfied with how well anti-hypertension medications control blood pressure at baseline, and how well the provider explains things at 12 months, increased the risk of having a worse SBP compared with people who did not feel satisfied with their hypertension medication and did not feel their provider explained things satisfactorily. Worse DBP at the end of the study was associated with feeling satisfied with hypertension medication at baseline, that their provider can explain things at the end of the study, and that providers can provide easy-to-understand answers to health care issues at the end of the study (Table 8-4). Better DBP at the end of the study was associated with baseline feelings of satisfaction with hypertension medication side effects and

how well a provider gives easy-to-understand answers to health care issues at the end of the study.

How respectful a patient felt a provider was at baseline, how satisfied a participant is that their provider gives easy-to-understand answers to health care issues at the end of the study, baseline feelings that hyperlipidemia medication was working, and that being satisfied with the side effects of their hyperlipidemia medication at baseline reduced the risk of having worse LDLc at the end of the study (Table 8-5). Being satisfied with their ability to plan when to take their hyperlipidemia medication at baseline, and how well their provider listened at baseline and the end of the study, increased the risk for a worse LDL.

Satisfaction Impact on Medication Adherence

Participants who rated their provider highly during the baseline visit were borderline significantly more likely to have better adherence to their diabetes medication at the end of the study compared with those who did not (Table 8-6). Participants who reported at the 12-month visit that they were satisfied with being able to plan when to take their diabetes medication and with how well their provider listened to them had worse adherence to their diabetes medication compared with people who did not feel satisfied (Table 8-6).

For blood pressure medication adherence, patients who reported at the 12-month visit that their providers had enough time were more likely to have worse adherence to blood pressure medication compared with people who did not feel their provider had enough time (Table 8-7). At baseline, participants who reported that they felt respected and that they were able to plan when to take their anti-hypertension medications were more likely to have better adherence to their blood pressure medication compared with those who felt disrespected by their provider or those who could not plan when to take their antihypertensive medications.

Those who had higher baseline anti-hyperlipidemia medication adherence and felt their provider was respectful at the end of the study were significantly more likely to have higher adherence at the end of the study (Table 8-8). Those who were satisfied with their provider's ability to explain issues at the end of the study were significantly less likely to improve at the end of the study. Satisfaction in planning anti-hyperlipidemia medication at the end of the study and baseline satisfaction how providers addresses medical issues, has enough time and provider's ability to explain also contributed to medication adherence.

8.5 DISCUSSION

This analysis illustrated that participants in the intervention group had overall significantly higher medication and clinician satisfaction compared with participants in the usual care group at the end of the study. Also, the results of this analysis identified how provider and medication satisfaction scores could affect medication adherence and clinical outcomes.

Except for two outcomes, randomization to the intervention group did not affect the odds of having better outcomes, as defined in this study. Participants in the intervention group were significantly more likely ($p=0.0012$) to have a better HbA1c at the end of the study compared with those in the usual care group. Group assignment did not affect the odds of having better SBP or DBP.

Clinician and Medication Satisfaction Variables that Positively Impacted Clinical Outcomes

For HbA1c, SBP, and LDLc, feeling respected by their provider lowered a participant's odds of having worse clinical outcomes compared with patients who did not feel respected. For

HbA1c and SBP, the more highly a provider was rated, the more likely it was that a participant had better clinical outcomes than participants who did not rate their providers' as highly. For SBP, DBP, and LDLc at the end of the study, if the provider was able to give easy-to-understand answers to health care issues, then their patients were less likely to have worse blood pressure and LDLc values. Participants who felt satisfied that their anti-hyperlipidemia and diabetes medications were working were more likely to have better HbA1c and LDLc values compared with those who did not feel satisfied. However, the opposite was true for blood pressure: participants who felt satisfied with their anti-hypertension medicine were more likely to have worse blood pressure clinical values compared with those who did not feel satisfied. Lastly, participants who were satisfied with the side effects of their anti-hypertension and anti-hyperlipidemia medications were more likely to have better clinical values than those who did not feel satisfied.

Clinician and Medication Satisfaction Variables that Negatively Impacted Clinical Outcomes

Some clinician and medication satisfaction variables increased the odds of a participant having worse clinical values at the end of the study. Patients who were satisfied that their provider listened to them were more likely to have worse HbA1c and LDLc values at the end of the study. Those who were satisfied that their provider was able to explain things in an way that was easy to understand were more likely to have worse blood pressure and LDLc values at the end of the study. Satisfaction with diabetes and anti-hypertension medications also increased the odds of having worse HbA1c and DBP at the end of the study. Additionally, being satisfied with the ability to plan when to take their anti-hyperlipidemia medication increased the odds of a having worse LDLc at the end of the study. Lastly, those who were satisfied that their provider

had enough time for them were more likely to have worse HbA1c at the end of the study compared with those who did not feel satisfied.

Clinician and Medication Satisfaction Variables that Positively Impacted Medication Adherence

For medication adherence, feeling respected by the provider increased the likelihood of having better adherence to blood pressure and anti-hyperlipidemia medications, and a higher overall rating of the provider increased the likelihood of adherence to diabetes medication. Being satisfied in their ability to plan on when to take their blood pressure and anti-hyperlipidemia medications also increased the likelihood of having a better adherence score. Those who felt satisfied in how their provider explained things at baseline, and that the provider had enough time for them, were also more likely to have a better anti-hyperlipidemia medication adherence score.

Clinician and Medication Satisfaction Variables that Negatively Impacted Medication Adherence

Unlike what was seen regarding adherence to blood pressure and anti-hyperlipidemia medications, participants who felt satisfied in their ability to plan when to take their diabetes medication were less likely to have a better diabetes adherence score. Being satisfied that their provider listened to them at the end of the study also decreased the odds of having better diabetes medication adherence. Regarding anti-hypertension medication adherence, those who felt that their provider had enough time for them were less likely to have a better adherence score to anti-hypertensive medication. Lastly, participants who felt that their provider gives easy-to-understand answers to health care issues at baseline, and who were satisfied in their provider's

ability to explain things at the end of the study, were less likely to have a better anti-hyperlipidemia medication adherence score.

It is important to note that the direction of the associations for the independent variables stayed consistent; at no time point was a covariate associated with both a positive and negative outcome. For example, while baseline satisfaction in a provider's ability to give easy-to-understand answers to health care issues was associated with both negative (worse DBP) and positive outcomes (better LDLc and SBP), it was only the *baseline* satisfaction that was associated with a negative outcome, while satisfaction at the *end* of the study was associated with positive outcomes. This is critical because it means that the associations stayed consistent within related outcomes. For example, having a highly-rated provider increased the odds of having better adherence to diabetes medication, and subsequently a better HbA1c at the end of the study; it did not positively affect one and negatively affect the other.

Positive patient-provider interaction, and its effect on adherence and clinical outcomes, have been previously documented ((279), (280), (274), (281)). Patients who feel an attachment to their provider are more likely to have better medication adherence and clinical outcomes ((274)). Interventions that support patient centered practice, involving the patient in care decisions, and treating them with respect, is an effective way to increase self-care behaviors and medication adherence ((280)). Patients who report being satisfied with their provider are more likely to comply with medication adherence, as well as with other self-care behaviors (275). In HIV patients, those who feel more respected by their provider are more likely to adhere to their medication regimen and to have better clinical outcomes (282).

Similar results were found in this analysis. Participants who felt respected, rated their provider higher, and felt their providers had enough time for them, and gave easy-to-understand

answers to health care issues, had better clinical outcomes than participants who did not feel likewise. Some provider covariates, like participant reporting feeling satisfied that the provider listened to them, were not related to improved outcomes. While listening techniques, such as engaged dialogue or being demonstratively attentive, have been recommended for physicians and are associated with higher provider satisfaction, no literature to date has found any effect on clinical or medication outcomes ((283), (284)). This could be due to variety of reasons. To our knowledge, no other study has used solely the AHRQ-CAHPS Clinician & Group Survey: Diabetes Clinic Satisfaction Survey to assess patient satisfaction with their provider. Instead, other studies have used more general questions, other sections of the CAHPS, or other survey methods to assess patient satisfaction with their provider ((283), (284)).

Satisfaction with prescribed medication has been associated with higher medication adherence, and through higher adherence, better clinical outcomes ((277), (282), (285)). Not only is medication satisfaction associated with better outcomes and adherence, lower medication satisfaction is associated with increased hypoglycemic symptoms and barriers to adherence to medication use ((286)). However, in our study, overall patient satisfaction with their medication did not increase the odds of positive outcomes, but rather trended towards decreasing the odds of better HbA1c and DBP. It is possible, in regards to HbA1c, that participants who were more satisfied with their medication were not on insulin, since insulin usage is associated with lower medication satisfaction(287; 288). Patients not on insulin may have had poorer diabetes control, but had not been prescribed insulin treatment yet. Previous studies show that patients who are dissatisfied with medication side effects, with the perceived side effects of their medications, or who do not tolerate their medication(s) are less likely to adhere to their medications ((289), (290), (281)). This was supported in our analysis, as participants who were satisfied with their

anti-hyperlipidemia or blood pressure medications were more likely to have higher adherence to their anti-hyperlipidemia and blood pressure medication. Others also report that patients who perceive that their medication is effective at controlling their conditions are more likely to be adherent ((291)). This was reflected by our results showing relationships between adherence to diabetes medications and improved HbA1c, but we did not see a similar effect on SBP.

There are limitations in this study that need to be addressed. First, due to concerns with patient burden and the questionnaires, a validated medication satisfaction instrument was not used. Instead, a short, four-question measure for each category of medication (diabetes, anti-hyperlipidemia and blood pressure) was implemented. This measure has not been validated. Second, the AHRQ-CAHPS Clinician & Group Survey: Diabetes Clinic Satisfaction Survey was designed to calculate a score for an individual provider, whereas we used it to assess individual factors; this could affect the validity of the measures and their associations with the outcomes.

This study, however, did have high retention rate with 91% of participants completing the study. Outcomes were either established clinical measures or the validated MMAS-8. Additionally, the REMEDIES 4D clinical trial was a novel intervention that placed CDEs in community-based primary care practices.

Studies show that a patient's health literacy and knowledge are related to provider and medication satisfaction (292-295); patients with better knowledge scores regarding diabetes and diabetes medication are more likely to adhere to their drug regimen compared with patients who had poorer diabetes knowledge(292). Additionally, patients whose providers test their recall and comprehension of new concepts about their diabetes care are more likely to have better HbA1c compared with patients whose recall and comprehension are not tested (293). These prior studies show that higher health literacy is significantly associated with better

medication/treatment adherence and better HbA1c(293; 296). Patients with adequate health literacy are not only better able to recognize symptoms of hypoglycemia, but also know how to treat themselves to correct hypoglycemia(297). Literacy was not measured in our study. However, since CDEs focus on patient education, it would be informative to determine if working with a CDE was associated with increased knowledge of diabetes. A future study in the area of CDEs in the primary care setting should include such a measure, to see whether CDE interaction has an effect on provider satisfaction and health outcomes.

In conclusion, this study illustrated that provider and medication satisfaction can affect clinical and medication adherence outcomes in the REMEDIES 4D trial. The results of this analysis identified aspects of provider and medication satisfaction that can be modified; these can help providers alter their behaviors in order to most effectively improve patient outcomes. . Also, the use of CDEs did not negatively affect clinical and treatment adherence outcomes in this population. The CDE-lead intervention group had a significantly higher proportion of patients who reported satisfaction with their provider at the end of the study, compared with those in the usual care group. Improvements in provider and medication satisfaction can lead to improved medication adherence and better clinical outcomes. Better clinical outcomes will not only reduce the economic burden of treating diabetes, but may reduce the risk and severity of diabetes complications in the future

8.6 TABLES AND LEGENDS

Table 8-1. Baseline characteristics of the REMEDIES 4D Population by study group

	Intervention		Usual Care		
	(n)	Mean (SD) or %	(n)	Mean (SD) or %	P-value
Age (years)	175	60.3 (10.2)	65	61.8 (10.8)	0.38
Gender					
Female	88	50.3	30	46.2	0.41
Male	87	49.7	35	53.8	
Race					
Non- Hispanic White	137	79.6	59	93.6	0.03
Non- Hispanic Black	29	16.8	4	6.3	
Other	4	2.3	0	0	
Diabetes duration (years)	170	12.2 (8.6)	63	10.7 (7.3)	0.17
Education					
High school/GED or less	64	37.6	21	33.3	0.54
College/technical school or higher	106	62.3	42	66.6	
Missing	5	2.9	2	3.1	
Smoking					
Never Smoke	76	44.7	35	58.3	0.16
Former Smoker	71	41.7	23	38.3	
Smoker	23	13.5	5	8.3	
Employment					
Employed	76	43.4	27	41.5	0.84
Unemployed	41	23.4	13	20.0	
Retired	49	28.0	20	30.8	
Missing	6	3.4	3	4.6	
Other	3	1.7	2	3.1	
Annual income					
Less than \$30,000	62	36.5	15	23.1	0.15
\$30,000 or higher	103	58.8	39	60.0	
Missing	5	4.5	9	16.9	
Health insurance *					

Table 8-1 (Continued)

Private insurance	114	66.2	38	60.3	0.39
Medicaid	14	8.1	5	7.9	0.95
Medicare ± Medicare Supplement	61	35.4	25	39.6	0.55
Other	9	5.2	4	6.3	0.74
No insurance	3	1.7	0	0%	0.56
Missing	3	1.7	3	4.6%	
HbA1c (%) / mmol/mol	175	8.8 (1.7) / 73 (18.6)	63	8.2 (1.4) / 66 (15.3)	0.007
Systolic blood pressure (mmHg)	175	129.1 (14.5)	63	133.6 (13.7)	0.03
Diastolic blood pressure (mmHg)	175	76.8 (7.8)	63	79.6 (9.3)	0.018
LDL cholesterol (mg/dL)	172	105.0 (40.0)	58	99.6 (35.2)	0.37
Hypertension					
Yes	122	71.7	43	68.2	0.69
Hyperlipidemia					
Yes	128	75.2	44	69.8	0.54
Microvascular complications[†]					
Yes	100	59.5	41	65.0	0.44
Macrovascular complications[‡]					
Yes	76	44.9	29	46.0	0.88
Depression severity[§]					(overall : 0.007)
None/minimal	68	39.5	32	50.0	0.15
Mild	49	28.4	18	28.1	0.94
Moderate	34	19.7	9	14.0	0.30
Moderately severe	20	11.6	1	1.5	0.01
Severe	1	0.5	4	6.2	0.02
Missing	3	1.7	0	0	

Continuous variables are displayed as mean (SD) and categorical variables are displayed as percentage.

Abbreviations: GED, general educational development; LDL, low-density lipoprotein.

* Patients may have more than one insurance plan.

† Microvascular complications included retinopathy, neuropathy, or nephropathy.

‡ Macrovascular complications included coronary heart disease, cerebrovascular disease, or peripheral vascular disease.

§ Depression severity was defined by PHQ-9 score: none/minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27).

Table 8-2 Mixed Model regression analyses, showing Associations between factors and HbA1c at end of study

Parameter	Coefficient	95% Confidence Interval	p-value
Intervention (Y/N)	-0.772	-1.23,-0.80	0.001
High School Education or less	0.428	0.002,0.85	0.048
Female Sex (Y/N)	0.291	-0.71, 0.112	0.160
Age yrs	-0.022	-0.05, -0.02	0.031
Baseline HbA1c (Continuous)	0.335	0.21,48	<.0001
Baseline Provider Rating	-0.534	-0.99, -0.09	0.019
Has Enough Time At 12 months (Y/N)	0.844	0.03,1.65	0.040
Respectful at 12 Months(Y/N)	-0.642	-1.47,0.17	0.125
Listens at Baseline(Y/N)	0.495	-0.03,0.99	0.062
Satisfaction with DM Meds at 12 Months(Y/N)	0.532	-0.15,-1.17	0.125
Satisfaction in how DM Meds work at 12 months(Y/N)	-0.625	-1.34,0.07	0.076

Table 8-3 Mixed Model regression analyses, showing Associations between factors and SBP at end of study

Parameter	Coefficient	95% Confidence Interval	p-value
Intervention (Y/N)	-0.070	-0.26,0.13	0.520
Baseline Provider Rating (Continuous)	0.183	-0.03, 0.40	0.10
Baseline SBP(Continuous)	0.017	0.01,0.02,	<0.0001
Baseline All Medication Satisfaction(Y/N)	-0.157	-0.32, 0.01	0.074
Addresses Medical Issues Well at 12 Months(Y/N)	-0.591	0.87 , -0.30	<0.0001
Respectful at End of Study(Y/N)	-0.136	-0.33, 0.06	0.18
Satisfaction in Provider's ability to explain at end of study(Y/N)	0.418	0.13 ,0.70	.004
Satisfaction in how HTN Meds work at Baseline(Y/N)	0.230	0.054, 0.40	.010

Table 8-4 Mixed Model regression analyses, showing Associations between factors and DBP at end of study

Parameter	Coefficient	95% Confidence Interval	p-value
Intervention (Y/N)	0.11	0.05, 0.2682	0.154
Age yrs	-0.006	-0.01, -0.0008	0.031
Baseline DBP (Continuous)	0.02	0.01, 0.02	<.0001
Addresses Medical Issues Well at 12 Months(Y/N)	-0.28	-0.50, -0.06	0.011
Addresses Medical Issues Well at Baseline(Y/N)	0.12	-0.01,0.27	0.084
Satisfaction in Provider's ability to explain at end of study(Y/N)	0.34	0.12, 0.56	0.001
Satisfaction in how HTN Meds work at 12 Months(Y/N)	0.20	-0.02, 0.43	0.081
Satisfied with HTN Side Effects at Baseline(Y/N)	-0.17	-0.40, 0.05	0.141

Table 8-5 Mixed Model regression analyses, showing Associations between factors and LDL at end of study

Parameter	Coefficient	95% Confidence Interval	p-value
Intervention (Y/N)	-0.06	-0.47,0.60	0.805
Male Sex (Y/N)	-0.89	-1.3- 0.43	0.0003
Addresses Medical Issues Well at 12 Months(Y/N)	-0.80	-1.65, 0.04	0.062
Respectful at Baseline(Y/N)	-0.89	-1.89,.04	0.061
Listens at Baseline(Y/N)	1.05	0.13, 1.96	0.024
Listen at 12 Months(Y/N)	1.19	0.33, 2.01	0.005
Ability to plan HPL Meds at 12 months(Y/N)	0.82	0.02,1.62	0.044
Satisfied with HPL Side Effects at Baseline(Y/N)	-0.65	-1.51,0.23	0.148
HPL Meds work at Baseline(Y/N)	-0.75	-1.49, 0.20	0.044

Table 8-6 Mixed Model regression analyses, showing Associations between factors and Diabetes Medication Adherence at end of study

Parameter	Coefficient	95% Confidence Interval	p-value
Intervention (Y/N)	0.22	-0.32, 0.78	0.438
Age yrs	0.01	0.004, 0.04	0.112
Baseline Provider Rating(Y/N)	0.46	-0.01, 0.94	0.056
Baseline Morisky(Continuous)	0.41	0.27, 0.55	<.0001
Satisfaction in Provider's ability to listen at end of study(Y/N)	-0.527	-1.02 ,0.02	0.041
Plan DM1(Y/N)	-0.37	-0.86, 0.11	0.135

Table 8-7 Mixed Model regression analyses, showing Associations between factors and Hypertension Medication Adherence at end of study

Parameter	Coefficient	95% Confidence Interval	p-value
Intervention (Y/N)	-0.89	-1.80, 0.009	0.052
Baseline HTN Morisky Adherence Score(Continuous)	0.454	0.31, 0.61	<0.0001
Has Enough Time at Baseline(Y/N)	-1.051	-2.14, 0.07	0.061
Respectful at Baseline(Y/N)	1.13	-0.07, 2.29	0.059
Satisfaction in planning Hypertension Medication at end of study(Y/N)	0.59	-0.12, 1.34	0.111

Table 8-8 Mixed Model regression analyses, showing Associations between factors and Hyperlipidemia Medication Adherence at end of study

Parameter	Coefficient	95% Confidence Interval	p-value
Intervention (Y/N)	-0.28	-0.94, 0.38	0.404
Baseline HPL Morisky Adherence Score(Continuous)	0.47	0.31, 0.63	<0.0001
Addresses Medical Issues Well at baseline(Y/N)	-0.76	-1.79, 0.26	0.1426
Has Enough Time at Baseline(Y/N)	-0.76	-1.72,0.19	0.105
Respectful at 12 months(Y/N)	1.06	0.07, 2.05	0.035
Baseline Satisfaction in Provider's ability to explain(Y/N)	0.82	0.27,-1.93	0.140
Satisfaction in Provider's ability to explain at end of study(Y/N)	-1.42	-2.39, -0.45	0.004
Satisfaction in planning Hyperlipidemia Medication at end of study(Y/N)	0.55	-0.04, 1.14	0.067

8.7 FIGURES

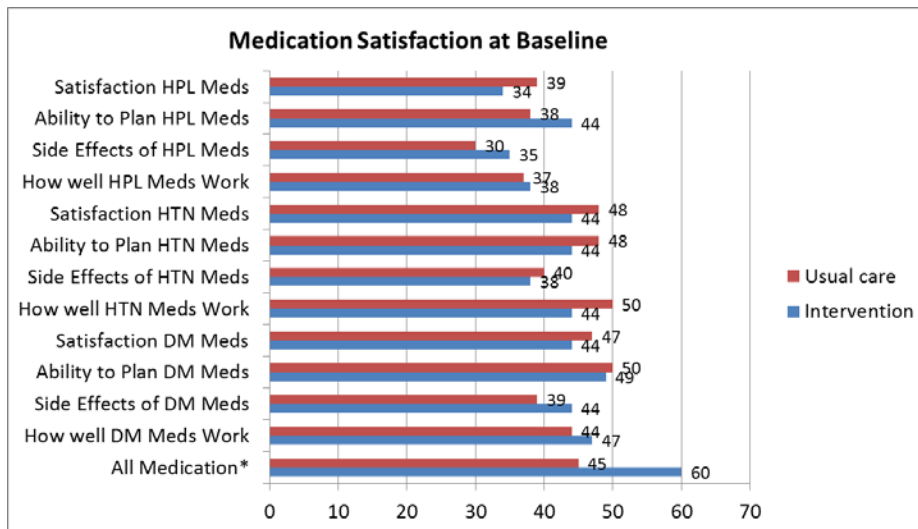


Figure 8-1 Differences in the Proportion of Patients Satisfied Medication Characteristics at Baseline in the REMEDIES 4D Population by Study Group

* Denotes p-value < 0.05

DM=Diabetes

HTN=Hypertension

HPL=Hyperlipidemia

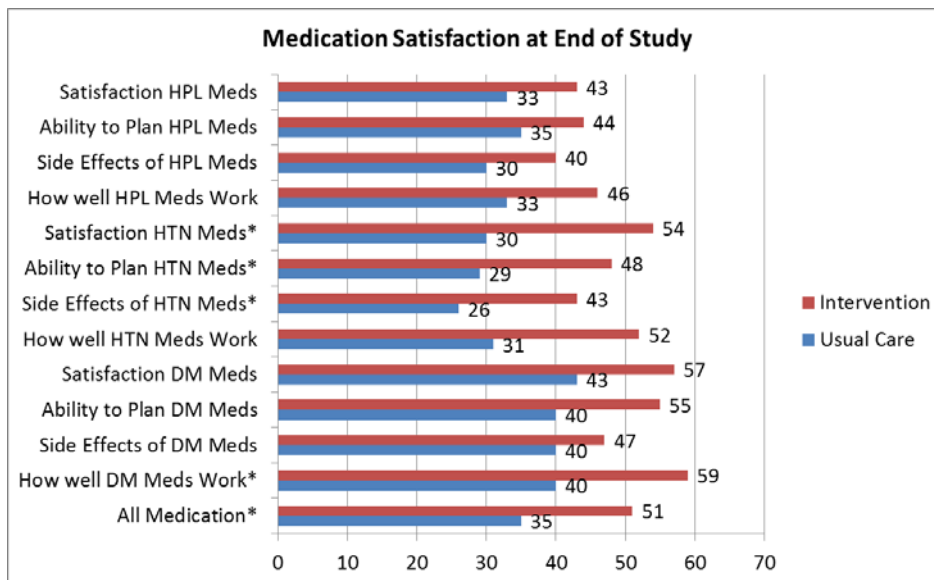


Figure 8-2 Differences in the Proportion of Patients Satisfied Medication Characteristics at End of Study in the REMEDIES 4D Population by Study Group

* Denotes p-value < 0.05

DM=Diabetes

HTN=Hypertension

HPL=Hyperlipidemia

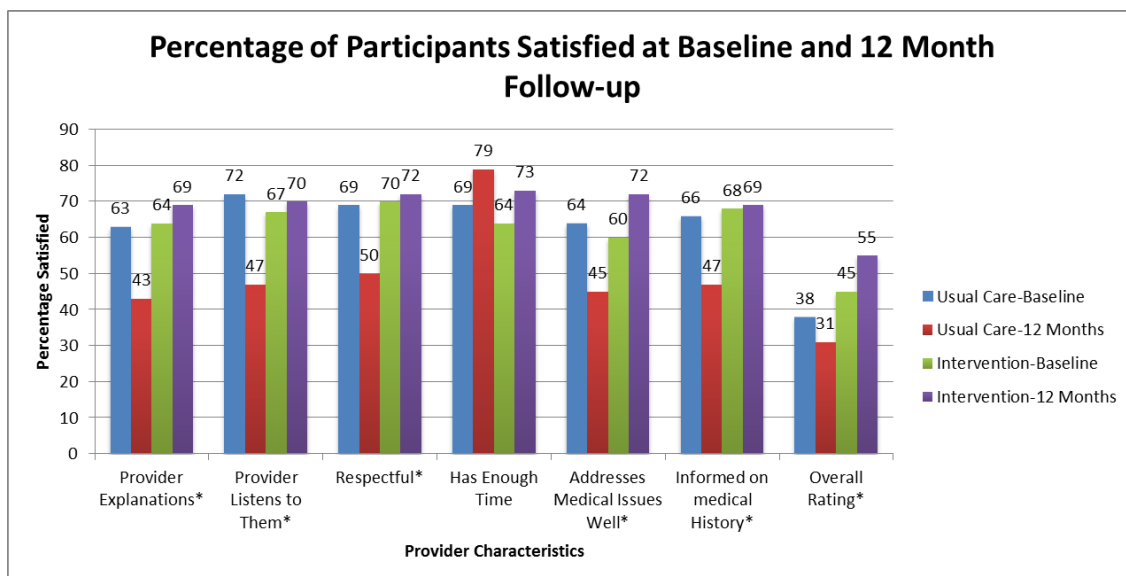


Figure 8-3 Differences in the Proportion of Patients Satisfied with Provider Characteristics at Baseline in the REMEDIES 4D Population by Study Group

* Denotes significant (p-value < 0.05) differences between groups at 12 month follow-up

DM=Diabetes

HTN=Hypertension

HPL=Hyperlipidemia

**9.0 MANUSCRIPT 3: IMPACT OF COGNITION ON IMPROVED DIABETES
MEDICATION ADHERENCE AND HBA1C USING CERTIFIED DIABETES
EDUCATORS (CDES) IN PRIMARY CARE**

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9.1 ABSTRACT

Objective: To assess relationships between cognitive performance with diabetes-care adherence and change in HbA1c, and, to identify factors that predict an increase in cognitive test scores using data from participants in the intervention arm of the REMEDIES 4D trial.

Research Design and Methods: This study conducted a longitudinal analysis that examined the baseline predictors of improvement in HbA1c, diabetes medication adherence, and increased cognition scores (The Montreal Cognitive Assessment Test, MoCa, and the Digit Symbols Substitution Test, DSST). Additionally, a cross-sectional analysis examining the associations between characteristics at the end of the study and improvement in HbA1c, diabetes medication adherence, and increased cognitive test scores was conducted

Results: There was not a significant relationship between cognitive performance with diabetes-care adherence and change in HbA1c. Provider's knowledge of diabetes and diabetes care, and no history of angiography or hyperlipidemia were associated with an increase in MoCA score at the end of the study. Increase in MoCA was related to increase in DSST, most likely because they both are measures of executive functions. Not feeling that diabetes took up too much physical and mental energy was borderline significant to increased DSST score.

Conclusions: Perceived diabetes distress, such as feeling unable to maintain a diabetes care routine, may be influence or be influenced by cognition. Since CDEs focus on clinical and behavioral factors, they can better support patients and possible reduce their diabetes distress.

9.2 INTRODUCTION

Diabetes is a large and growing public health concern, both worldwide and in the United States. In 2014, the Centers for Disease Control and Prevention estimated that 9.3% of US adults ages 18 and over, which equates to 29.1 million Americans, have diabetes, and approximately one-fourth are undiagnosed(6). By 2050, an estimated 33% of adults in the United States will have diabetes(7). With this increase in the number of people with diabetes, the number of complications related to the disease will likely increase as well. There are numerous micro- and macrovascular complications associated with hyperglycemia. Previous large clinical trials, such as United Kingdom Prospective Diabetes Study (UKPDS), show that in adults with type 2 diabetes, each 1% reduction in glycated hemoglobin (HbA1c) is related to a 35% reduction in the risk of developing microvascular complications, with a 25% reduction in the number of diabetes-related deaths, and with an 18% reduction in the risk of myocardial infarction(175; 269).

A growing area of research in type 2 diabetes is the effect of chronic hyperglycemia on cognitive function . People with diabetes are more likely to experience cognitive dysfunction than similarly-aged people without diabetes(298-302). Although the exact mechanisms underlying poor cognitive function in people with diabetes remain unclear, generalized brain gray matter atrophy and loss/damage of cerebral white matter in those with diabetes appears to be related to increased HbA1c(298; 303). Higher HbA1c levels and poorly-controlled diabetes are associated with lower scores on a number of cognitive tests(304-307). Even in non-diabetic patients, higher HbA1c is associated with poorer cognitive performance(304). Encouragingly, there is evidence suggesting that a reduction in HbA1c can slow or improve cognitive dysfunction (304; 305; 308).

Improving glycemic control improves diabetes patient's quality of life and reduces their risk for complications(12). Many factors contribute to clinical outcomes, one of which is adherence to prescribed medication therapies(309). Those with low medication adherence are significantly less likely to have their anti-diabetes medication intensified despite elevated HbA1c compared to those with high medication adherence(310). Additionally, good adherence is associated with a 10% lower HbA1c value compared to those with poor adherence(270). Self-care measures, including adherence to diabetes medication, is significantly correlated with working memory and executive function(140). In one study a participant's scores on the cognitive assessment Executive Interview 25 mediated the relationship of HbA1c and self-care measures (311). While adherence can be difficult to measure, the Morisky Medication Adherence Scale-8 is an effective, cost and time efficient way to estimate adherence and has a sensitivity of 61% compared to the gold standard of prescription claims data (248; 312).

The REdesigning MEDication Intensification Effectiveness Study for Diabetes (REMEDIES 4D) was a 12-month, patient centered, intervention trial to test whether the use of certified diabetes educators (CDEs) to provide diabetes education and intensify treatment, using preapproved, evidence-based protocols, would improve medication adherence and clinical measures. The objective of the current analysis was twofold. First, to assess relationships between cognitive performance with diabetes-care adherence and change in HbA1c, and second, to identify factors that predict an increase in cognitive test scores using data from participants in the intervention arm of the REMEDIES 4D trial.

9.3 MATERIALS AND METHODS

The materials and methods for the REMEDIES 4D trial have been detailed in a previous publication and will only be briefly discussed (263).

Participants

The REMEDIES 4D trial was a clustered, randomized, clinical trial; 15 primary care practices in Southwest Pennsylvania were randomized to either intervention or usual care groups (8 were randomized to intervention, 7 to usual care/control). . Participants were screened and consented between July 2012 and January 2014. Eligible patients had to be age 18 years or older; have a diagnosis of type 2 diabetes for at least one year prior to study baseline; have made at least one visit to their primary care provider within the last 12 months; and have at least one of their most recent clinical values for HbA1c ($\geq 7\%$ / 53 mmol/mol), blood pressure (SBP ≥ 140 mm/Hg or DBP ≥ 80 mm/Hg), or LDLc (≥ 100 mg/dL) above goal. Exclusion criteria included patients who were not ambulatory; had gestational diabetes; were pregnant or planning on becoming pregnant during the course of the study; had a scheduled surgery; were on dialysis; unable to read or comprehend English; or had a diagnosis of cognitive impairment. By the end of recruitment, 175 patients were enrolled in the intervention group and 65 were enrolled in the control group. The population was 50.8% male, 79% non-Hispanic white, with a mean age of 61 years of age. Primary outcomes of main study were HbA1c, SBP, SBP, and LDLc values at the end of the study as well as examining the proportion of patients whose medication was intensified throughout the study. Compared with the usual care group, those in the intervention group were significantly more likely to have a lower HbA1c at the end of the study and more likely to have their diabetes medication intensified (unpublished data).

Substudy

Only the intervention group was used in this substudy. Compared with the usual care group, the intervention group was more likely to have a higher HbA1c at baseline. This was due to missing cognitive data in the usual care group that precluded the ability to conduct valid statistical analyses. This study conducted a longitudinal analysis that examined the baseline predictors of improvement in HbA1c, diabetes medication adherence, and increased cognition scores. Additionally, a cross-sectional analysis examining the associations between characteristics at the end of the study and improvement in HbA1c, diabetes medication adherence, and increased cognitive test scores was conducted.

Intervention

During the REMEDIES 4D trial, certified diabetes educators (CDEs) provided the intervention group with diabetes education and intensified treatment over a one year intervention period, using preapproved, evidence-based protocols. Protocols were derived from evidence-based guidelines that were available at the start of the study in 2012 and these were updated throughout the trial as the evidence changed. The control group continued to see their primary care physician; they were also invited to attend monthly patient-centered diabetes support groups, led by a CDE. In addition to extracting HbA1c, LDLc, blood pressure, and medication data from the electronic health record (EHR) for both the intervention and usual care groups, demographic, medication use, self-care activities(265), treatment satisfaction, medication adherence(248), cognitive status(250; 252), and depression(249) information was collected via completed surveys. Participants were also asked questions regarding their medical history, to determine the prevalence of over thirty comorbidities at baseline, and the incidence of comorbidities throughout the study. Many of these comorbidities were consolidated into

categories for analysis. For example, “being diagnosed with ophthalmic complications (diabetic retinopathy; diabetic eye disorders)” and “Laser photocoagulation for diabetic neuropathy (diabetic eye disease)” were combined to create the variable “retinopathy”. Patients were also asked to fill out the Diabetes Distress Scale (DDS-17) (30). This screener asked patients to rate 17 areas regarding how living with diabetes impacts their life (e.g., “Feeling that diabetes is taking up too much of my mental and physical energy everyday”), as well as their feelings about their diabetes care provider (e.g., “Feeling that my doctor doesn’t know enough about diabetes and diabetes care”). Participants also filled out the AHRQ-CAHPS* Clinician & Group Survey: Diabetes Clinic Satisfaction Survey, asking them about their relationship and satisfaction with their diabetes care provider(247). Participants rated their provider overall and were also asked questions pertaining to more specific areas, such as if they felt respected by their provider, if the provider was able to convey treatment information, and if they felt their provider was well informed about their personal health history and diabetes care (247).

Outcome Measurements

The primary outcomes were improvement in HbA1c (i.e., a reduction in HbA1c from baseline, yes/no);improvement in anti-hyperglycemia medication adherence (yes/no), and an increase in cognitive test scores (yes/no) at the end of the one-year intervention period. Clinical values were extracted from the participant’s EHR. Clinical values could be extracted up to one year in advance of the baseline visit and there was a one month window, either before or after the 12-month follow-up visit, when values could be retrieved. “Improvement” was defined as a reduction in HbA1c at 12 months compared to baseline. The Morisky Medication Adherence Scale-8 (MMAS-8) was used to measure participant adherence to their anti-hyperglycemia medication, and was included in the survey at baseline and at the 12-month visit. The answers to

the MMAS-8 were converted to an adherence scale (<6 = low adherence; $6-<8$ = medium adherence; 8 = high adherence), and “improvement” was defined as an increase in adherence level. Cognitive performance was assessed using the Montreal Cognitive Assessment (MoCA) and the Digit Symbol Substitution Test (DSST; number correct in 90 seconds); these tests were administered at baseline and at the 12-month follow-up. An increase in either the MoCA or DSST score at 12-months was considered a positive change.

Statistical Analysis

Descriptive statistics, including distributions and frequencies, were performed on all outcome measurements. Spearman and Pearson correlation coefficients were used to identify associations between independent variables and covariates not already identified from the literature; these correlations were also used to investigate possible multicollinearity between covariates. Linear mixed models (procedure Glimmix in SAS) for longitudinal data were used to evaluate associations between the independent and outcome variables; these models adjust for the correlation of patients within practice and also account for the correlation of the repeated measurements. All covariates were analyzed in univariable mixed models, and those with a p-value ≤ 0.1 were considered eligible for the final model. Backwards stepwise regression was used to create the final mixed models, with covariates ≤ 0.05 kept in the model. All cognitive outcomes were adjusted for age and education due to strong evidence supporting that age and education affect cognition (255; 256). All analyses were carried out using the SAS statistical software system, version 8.3, SAS Institute Inc., Cary, NC.

9.4 RESULTS

Demographic information is reported in Table 9-1. Average participant age was 60.3 years (29-87); 49.7% were male and 79.6% were non-Hispanic whites. On average, participants had a diabetes duration of 12.2 years at the beginning of the study, with an average HbA1c of 8.8%. The proportions of those who had an improved or increased outcome are shown in Figure 1.

Improvement in HbA1c

The results of the longitudinal univariable analysis for HbA1c improvement are reported in Table 9-2. Factors that statistically significantly predicted HbA1c improvement at 12 months ($p \leq 0.05$) were: having more than a high school education; being male; and having a higher baseline HbA1c. Some patient-provider variables were also significantly related to HbA1c improvement, namely: participants reporting that their health care provider could explain their disease to them; that their provider respected them as a person; that their provider was able to give adequate information on health care; and participants reporting a high overall rating of their provider. More frequent self-blood glucose monitoring was also significantly associated with improved HbA1c. Factors with a p-value between 0.05 and 0.10 were also tested in the multivariable model. In the final multivariable model (Table 9- 3), higher HbA1c at baseline, and a highly-rated health care provider were associated with improvement of HbA1c at the end of the study while testing blood glucose more than three times a day was significantly associated with no improvement in HbA1c at the end of the study.

For the cross-sectional univariable analysis, improved LDLc, improved SBP, feeling respected by their health care provider, and not feeling overwhelmed by the demands of living with diabetes were significantly associated with improved HbA1c at the end of the study (Table

9- 4). In the multivariable model (Table 9-5), having an improved LDLc or SBP, not feeling overwhelmed by their diabetes, and feeling respected by their health care provider were significantly associated with an improvement in HbA1c at the end of the study.

Improvement in Anti-Hyperglycemia Medication Adherence

The results of the longitudinal univariable analysis for improvement in diabetes medication adherence level are reported in Table 9-6. Responses of being in overall in good health, of not feeling overwhelmed by their diabetes, or of not feeling that their diabetes took up too much physical and mental energy were eligible for consideration in the final model. In the final model, however, (Table 9-7), not feeling overwhelmed by their diabetes remained significantly associated with improved diabetes medication adherence.

Cross-sectionally, better self-perceived health status, higher self-reported adherence to anti-hypertension medication, and lower diabetes distress (i.e., not feeling overwhelmed by their diabetes) were available for the final model (outcome = improved adherence to diabetes medication, Table 9- 8). Only higher self-reported adherence to anti-hypertension medication was significantly associated with better diabetes medication adherence in the final model (Table 9-9).

Increase in MoCA score

Improvement in adherence to diabetes medications or improvement in HbA1c associated were not associated with an increase in MoCA score. In the univariable longitudinal analysis (Table 9- 10), no reported history of hyperlipidemia, and angiography were associated with an increase in MoCA scores. Additionally, feeling like your provider does know enough about diabetes and diabetes care was associated with increased MoCA score. In the multivariable model (Table 9-11), provider's knowledge of diabetes and diabetes care, and no history of

angiography or hyperlipidemia were associated with an increase in MoCA score at the end of the study. In the cross-sectional model (Table 9-12), reports of feeling that their doctor could adequately explain their diabetes care, and having a reduction in DBP, were associated with increased MoCA scores. In the multivariable model, only an increase in DSST score and a reduction in DBP remained significantly related to increase in MoCA score (Table 9-13). All models were adjusted for age and education.

Increase in DSST score

Adherence to diabetes medications or improvement in HbA1c associated were not associated with an increase in DSST score. In the longitudinal model, female sex and reporting a history of transient ischemic attacks (TIA) at baseline were eligible for consideration in the final longitudinal model (Table 9-14). In the multivariable model, neither of these variables remained statistically significantly related to increase in DSST score.

Cross-sectionally, an increase in MoCA score and not feeling that diabetes took up too much physical and mental energy were associated with an increase in DSST score at the end of the study (Table 9-15). Having an increase in MoCA score was significantly associated with increased DSST score; not feeling that diabetes took up too much physical and mental energy was borderline significant ($p=0.051$) (Table 9-16). Similar to previous analysis, all models were adjusted for age and education.

9.5 DISCUSSION

This analysis was able to identify possible predictors and associations with improvement in HbA1c, diabetes medication adherence and an increase in cognitive test scores among participants of the intervention group of the REMEDIES 4D clinical trial

Significant predictors of improvement in HbA1c at the end of the study included higher HbA1c at the beginning of the study, a highly-rated health care provider, and testing blood glucose less than three times a day at baseline. At the end of the study, improvement in HbA1c was significantly associated with improvement in LDLc and SBP as well as not feeling overwhelmed by their diabetes and feeling respected by their health care provider. Lower diabetes distress at baseline predicted increased adherence to diabetes medication at the end of the study and higher adherence to anti-hypertension medication were associated with increased adherence to diabetes medication at the 12-month visit.

We found no relationship between diabetes medication adherence or HbA1c improvement and increases in MoCA or DSST scores. The provider's knowledge of diabetes and diabetes care, and absence of a history of an angiogram procedure or hyperlipidemia at baseline, predicted increased MoCA scores. Those who had an increase in MoCA score also experienced an increase in their DSST score, as well as a reduction in their DBP, from baseline. For DSST, no variables predicted an increase at the end of the study; in the multivariable model, only increase in MoCA was significantly associated with an increase in DSST, although not feeling that diabetes took up too much physical and mental energy was borderline significant.

In both the cross-sectional and longitudinal analyses, improved HbA1c was associated with certain participant-rated aspects of their health care provider. Previous research has primarily emphasized the patient portion of the patient-provider relationship, but there are some

studies that look at the provider or the patient-provider relationship as a whole and its effect on clinical outcomes(283; 284; 293; 313; 314). Positive relationships and engaged communication between provider and patient are found to be significantly correlated with better physiologic outcomes in patients with hypertension, diabetes, stomach ulcers, and breast cancer(315). In cross-sectional analysis of HIV patients, those who report that their provider treats them with respect are more likely to be on appropriate antiretroviral treatments and to have undetectable serum HIV RNA(282). Diabetes patients who rate their providers' level of practical support, such as setting treatment goals and providing a written care plan highly, are significantly more likely to have lower HbA1c at follow up(316). Diabetes patients whose providers talk effectively communicate with them, and assess their recall and treatment comprehension, are more likely to improve their HbA1c compared with patients whose providers do not act thusly (317). Additionally, people with diabetes who feel less attached to their providers and rate their patient-provider communication as poor, are significantly more likely to have a higher HbA1c compared with their counterparts who report a better patient-provider relationship(274).

Lower diabetes distress can also influence diabetes medication adherence and HbA1c. Previous studies show that psychosocial factors greatly influence clinical outcomes and self-care measures, such as medication adherence (275; 276; 318; 319). Patients with lower diabetes-related emotional distress, who feel in control of their diabetes, are more likely to have better treatment adherence and glycemic control than those with higher distress (318). In a 6-month intervention aimed at increasing participation in diabetes self-management education, those with a decrease in diabetes distress, independent of depression, saw an improvement in their HbA1c since baseline (319).

The positive correlation of HbA1c with cholesterol has been previously documented in the literature (320-322). In both Chinese and Saudi Arabian populations, cholesterol levels predict HbA1c and vice versa, so the reduction in HbA1c and LDLc are consistent with this correlation (320; 322). The association of improved SBP and improved HbA1c may be linked to reduced diabetes distress. People with lower distress have better self-management behaviors, including taking their medications as prescribed. They may also have reduced stress, which can lower blood pressure levels (323). Also, since hyperinsulinemia and increased exchangeable sodium is common in those with diabetes, the reduction of HbA1c, and correspondingly decreased insulin levels, may also impact SBP in those with diabetes (324).

Diabetes distress has been previously shown to have no association with cognition (325). This finding could be due, in part, to the recent recognition that diabetes distress is independent of major depressive disorder, and major depressive disorder is a common comorbidity in people with mild cognitive impairment (326-329). In our study, depression scores were not significantly associated with an increase in cognitive test scores, either in longitudinal or cross-sectional models.

The relationship between change in cognitive test scores and a the absence of hyperlipidemia or an angiography is consistent with the literature. Hyperlipidemia is a known risk factor for cardiovascular disease and mild cognitive impairment (326; 330-332). There is evidence showing that those who undergo angiography perform worse on cognitive tests compared with patients not having angiography (333). This could be due to the fact that people with cardiovascular disease are more likely to have an angiogram, and cardiovascular disease is a risk factor for cognitive impairment (2).

MoCA measures a number of cognitive functions, including executive function, attention, memory and psychomotor speed (334), while the DSST primarily assesses psychomotor speed(335). Given some degree of overlap between the domains assessed by these two tests, it is not surprising that increases in MoCA and DSST scores track together.(336).

There are some limitations that need to be addressed. Due to missing data, this analysis was not able to determine if there was a difference between the usual care group and the intervention group for the outcomes of interest. The follow-up period for the REMEDIES study was only 12 months which may be too short a period to detect any significant changes in cognitive test scores. Also, since the improvement measures were dichotomous (yes/no), there may have been some degree of improvement, however we were unable to detect it. Lastly, there could be respondent bias regarding medication adherence; participants may overstate their degree of adherence which would obscure the true relationships between adherence and cognitive test scores.

In conclusion, this analysis identified predictors of improvement for HbA1c, diabetes medication adherence, and increased cognitive test scores in a population of middle-aged adults with type 2 diabetes; CDEs delivered patient-centered education to these participants. Since CDEs focus on clinical and behavioral factors, they can better support patients' behavioral and clinical goals, and possibly reduce their diabetes distress. This is crucial because lower diabetes distress was associated with improved HbA1c, diabetes medication adherence, and increased cognitive test scores. If the use of CDEs in the primary care practice setting can lead to a reduction in patient's diabetes distress, then patients may be better able to handle their medication regime and their diabetes. This in turn may possibly lead not only to a reduction in micro-and macrovascular complications, but also to a reduction or delay in cognitive

dysfunction, t since uncontrolled diabetes is related to a higher risk of cognitive dysfunction. Maintaining cognitive function can lead to a better quality of life for people with diabetes as well as reduce the economic burden associated with cognitive impairment and type 2 diabetes complications (337).

9.6 TABLES AND LEGENDS

Table 9-1 Baseline Characteristics of REMEDIES 4D Population

	Number of Intervention patients for analysis	Mean (SD) or percentage
Age (years)	175	60.3 (10.2)
Gender		
Female	88	50.3
Male	85	49.7
Race		
White	137	79.6
Black	29	16.8
Other	4	2.3
Diabetes duration (years)	170	12.2 (8.6)
Education		
High school/GED or less	64	37.6
College/technical school or higher	106	62.3
Missing	5	2.9
Smoking		
Never Smoke	76	44.7
Former Smoker	71	41.7
Smoker	23	13.5
Employment		
Employed	76	43.4
Unemployed	41	23.4
Retired	49	28.0
Missing	6	3.4
Other	3	1.7
Annual income		
Less than \$30,000	62	36.5
\$30,000 or higher	103	58.8
Missing	5	4.5

Table 9-2 (Continued)

Health insurance *		
Private insurance	114	66.2
Medicaid	14	8.1
Medicare ± Medicare Supplement	61	35.4
Other	9	5.2
No insurance	3	1.7
Missing	3	1.7
HbA1c (%)	175	8.8 (1.7)
Systolic blood pressure (mmHg)	175	129.1 (14.5)
Diastolic blood pressure (mmHg)	175	76.8 (7.8)
LDL cholesterol (mg/dL)	172	105.0 (40.0)
Hypertension		
Yes	122	71.7
Hyperlipidemia		
Yes	128	75.2
Microvascular complications[†]		
Yes	100	59.5
Macrovascular complications[‡]		
Yes	76	44.9
Depression severity[§]		
None/minimal	68	39.5
Mild	49	28.4
Moderate	34	19.7
Moderately severe	20	11.6
Severe	1	0.5
Missing	3	1.7

Continuous variables are displayed as mean (SD) and categorical variables are displayed as percentage.

Abbreviations: GED, general educational development; LDL, low-density lipoprotein.

* Patients may have more than one insurance plan.

[†] Microvascular complications included retinopathy, neuropathy, or nephropathy.

[‡] Macrovascular complications included coronary heart disease, cerebrovascular disease, or peripheral vascular disease.

[§] Depression severity was defined by PHQ-9 score: none/minimal (0–4), mild (5–9), moderate (10–14), moderately severe (15–19), and severe (20–27).

Table 9-3 Longitudinal Univariable Analyses for Improvement in HbA1c Over the 12-month Intervention Period

Variable	OR	95% CI	P-Value
Depression			0.28
No/Mild Depression (0-9)	(Referent)	(Referent)	
Moderate Depression (10-14)	0.49	0.16-2.15	0.11
Severe Depression (15-27)	0.60	0.22-1.17	0.43
Schooling			
High School Education or Less	Referent	Referent	
>High School	1.40	0.97-4.48	0.059
Female	0.41	0.18-0.92	0.029
Health Care Provider's Ability to Explain	2.48	1.01-6.11	0.067
Feeling Respected by Health Care Provider	2.31	0.97-5.5	0.057
Health Care Provider's Knowledge of Diabetes	2.33	1.01-5.36	0.046
Rating of Health Care Provider	1.23	1.04-1.46	0.013
# of times blood glucose is tested per day			0.023
None	Referent	Referent	
1-3	1.36	0.52-3.38	0.51
3+	0.42	0.16-1.09	0.75
Baseline HbA1c	1.15	1.11-1.92	0.072
Baseline DSST score*	1.02	0.98-1.06	0.30
Baseline MoCA score*	0.97	0.87-1.09	0.71

*Adjusted for Age, Sex, Education

Table 9-4 Longitudinal Multivariable Analyses for Improvement in HbA1c Over the 12-month Intervention Period

Variable	OR	95% CI	P-value
Rating of Health Care Provider	1.23	1.03-1.49	0.012
Baseline HbA1c	1.49	1.09-1.49	0.020
# of times blood glucose is tested per day			0.12
None	Referent	Referent	
1-3	1.18	0.41-3.40	0.74
3+	0.31	0.10-.92	0.034

Table 9-5 Cross Sectional Univariable Analyses for Improvement in HbA1c Over the 12-month Intervention Period

Variable	OR	95% CI	P-Value
Improved LDL	4.01	1.85-8.75	0.0005
Improved SBP	0.33	0.13-1.01	0.052
Depression			0.21
No/Mild Depression (0-9)	(Referent)	(Referent)	
Moderate Depression (10-14)	0.58	0.23-1.43	0.23
Severe Depression (15-27)	0.31	0.07-1.39	0.13
Feeling Respected by Health Care Provider	4.48	1.56-12.18	0.005
HCP_listen Feeling that Health Care Provider Listens to Your Concerns	2.03	0.72-5.47	0.17
Done work or other activities less carefully than usual due to emotional problems?	1.99	0.71-5.47	0.88
Distressed by the demands of living with diabetes.	0.71	0.53-0.95	0.023
MoCa Score at End of Study	1.08	0.96-1.21	0.19
DSST-90 Score at End of Study	1.02	0.99-1.06	0.14

Table 9-6 Cross Sectional Multivariable Analyses for Improvement in HbA1c Over the 12-month Intervention Period

Variable	OR	95% CI	P-value
Improved LDL	5.72	1.80-16.30	0.0034
Improved SBP	0.11	0.02-0.55	0.0075
Feeling Respected by Health Care Provider			0.014
Always	(Referent)	(Referent)	
Usually	0.16	0.05-0.53	0.038
Sometimes	0.54	0.06-4.95	0.97

Table 9-7 Longitudinal Univariable Analyses for Improvement in Diabetes Medication Adherence Over the 12-month Intervention Period

Variable	OR	95% CI	P-Value
Depression			0.60
No/Mild Depression (0-9)	(Referent)	(Referent)	
Moderate Depression (10-14)	0.81	0.38-1.68	0.56
Severe Depression (15-27)	0.55	0.18-1.76	0.32
Baseline DSSTscore *	1.02	0.92-1.13	0.68
Baseline MoCA score*	1.01	0.98-1.05	0.38
Patient Reported Health Status	1.66	0.53-4.90	0.10
Health Care Provider's Ability to Explain	1.59	0.89-5.40	0.27
Rating of Health Care Provider	1.09	0.92-1.29	0.28
Feeling that diabetes is taking up too much of my mental and physical energy every day.	2.03	0.80-4.90	0.084
Feeling that I am not testing my blood sugars frequently enough.	1.22	0.47-3.15	0.17
Feeling overwhelmed by the demands of living with diabetes.	2.40	1.02-5.70	0.044
Not feeling motivated to keep up my diabetes self management.	0.63	0.30-1.41	0.48
Average Diabetes Distress	0.93	0.63-1.36	0.70
Schooling			
High School Education or Less	Referent	Referent	
>High School	1.08	0.51-2.33	0.83

*Adjusted for Age, Sex, Education

Table 9-8 Longitudinal Model for Improvement in Diabetes Medication Adherence Over the 12-month Intervention Period

Variable	OR	95% CI	P-value
Feeling overwhelmed by the demands of living with diabetes.	2.4	1.02-5.7	0.044

Table 9-9 Cross Sectional Univariable Analyses for Improvement in Diabetes Medication Adherence Over the 12-month Intervention Period

Variable	OR	95% CI	P-Value
MoCA Score at End of Study	1.02	0.90-1.14	.72
DSST Score at End of Study	1.02	0.99-1.06	0.14
No/Mild Depression (0-9)	(Referent)	(Referent)	0.57
Moderate Depression (10-14)	0.63	0.25-1.58	0.33
Severe Depression (15-27)	1.22	0.29-4.90	0.78
Averaged Diabetes Distress	1.01	0.88-1.61	0.79
Feeling that Health Care Provider has Enough Time for You.	0.62	0.34-2.11	0.45
Patient Reported Health Status	0.09	0.01-1.17	0.10
Health Care Provider's Knowledge of Diabetes	0.51	0.16-1.60	0.20
Feeling that Health Care Provider Listens to Your Concerns	0.55	0.24-1.73	0.53
Rating of Health Care Provider	0.96	0.69-1.30	0.78
How often you felt down in last week	0.44	0.18-1.10	0.43
Feeling that diabetes is taking up too much of my mental and physical energy every day.	0.99	0.34-2.82	0.79
Feeling that I am not testing my blood sugars frequently enough.	0.79	0.27-2.50	0.83
Feeling overwhelmed by the demands of living with diabetes.	0.43	0.14-1.31	0.26
Not feeling motivated to keep up my diabetes self management.	0.68	0.22-2.00	0.43
Baseline HbA1C	0.86	0.63-1.16	0.31
Summed Hypertension Morisky Score	1.40	1.14-1.71	0.001
Improved SBP	1.37	0.44-4.30	0.57
Improved DBP	0.77	0.30-2.07	0.61
How Often Do You Eat a Good Diet?	1.04	0.81-1.34	0.71

Table 9-10 Cross Sectional Model for Improvement in Diabetes Medication Adherence Over the 12-month Intervention Period

Variable	OR	95% CI	P-value
Summed Hypertension Morisky Score	1.40	1.14-1.71	0.001

Table 9-11 Longitudinal Univariable Analyses for Increase in MoCA Score Over the 12-month Intervention Period*

Variable	OR	95% CI	P-Value
Depression			0.65
No/Mild Depression	(Referent)	(Referent)	
Moderate Depression	0.96	0.47-1.95	0.91
Severe Depression	0.60	0.20-2.82	0.37
No history of Hyperlipidemia (Y/N)	2.43	1.01-5.80	0.045
No history of Angiography (Y/N)	3.12	1.27-7.70	0.013
Health Care Provider's Knowledge of Diabetes	1.56	0.69-3.30	0.30
Feeling that my doctor doesn't know enough about diabetes and diabetes care.	0.22	0.10-0.75	0.024
Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.	0.35	0.10-0.76	0.23
Feeling that my doctor doesn't take my concerns seriously enough.	0.41	0.06-2.55	0.34
Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	0.81	0.20-3.30	0.76
History of Retinopathy	3.32	1.07-11.02	0.03

* All Analyses Adjusted for Age and Education

Table 9-12 Longitudinal Multivariable Analyses for Increase in MoCA Score Over the 12-month Intervention Period*

Variable	OR	95% CI	P-value
Feeling that my doctor doesn't know enough about diabetes and diabetes care.			0.010
Not a problem	(Referent)	(Referent)	
Slight problem	0.30	0.06-1.19	0.086
A problem	0.02	0.04-0.60	0.007
No History of Angiography (Y/N)	4.05	1.53-11.02	0.005
No History of Hyperlipidemia (Y/N)	3.12	1.23-8.00	0.017

* All Analyses Adjusted for Age and Education

Table 9-13 Cross Sectional Univariable Analyses for Increase in MoCA Score Over the 12-month Intervention Period*

Variable	OR	95% CI	P-Value
Depression			0.58
No/Mild Depression	(Referent)	(Referent)	
Moderate Depression	1.12	0.48-2.63	0.77
Severe Depression	0.47	0.10-2.27	0.34
Rating of Health Care Provider	1.15	0.83-1.58	0.37
Increase in DSST Score at End of Study	3.12	1.43-6.80	0.004
Health Care Provider's Knowledge of Diabetes	1.8	0.81-4.05	0.14
Health Care Provider's Ability to Explain	3.28	1.01-9.97	0.04
Feeling that my doctor doesn't know enough about diabetes and diabetes care.	0.80	0.03-18.10	0.88
Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.	1.29	0.12-13.4	0.82
Feeling that my doctor doesn't take my concerns seriously enough.	0.91	0.16-4.95	0.99
Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	1.08	0.16-9.02	0.48
SBP at end of Study	0.99	0.95-1.01	0.20

* All Analyses Adjusted for Age and Education

Table 9-14 Cross Sectional Model for Increase in MoCA Score Over the 12-month Intervention Period*

Variable	OR	95% CI	P-value
No Improvement in DSST	0.33	0.16-0.80	0.013

* All Analyses Adjusted for Age and Education

Table 9-15 Longitudinal Univariable Analyses for Increase in DSST Score Over the 12-month Intervention Period*

Variable	OR	95% CI	P-Value
Depression			0.27
No/Mild Depression	(Referent)	(Referent)	
Moderate Depression	1.75	0.86-3.32	0.11
Severe Depression	1.20	0.40-3.59	0.73
Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	0.71	0.20-2.63	0.17
Not feeling motivated to keep up my diabetes self-management.	1.17	0.55-2.45	0.43
Female Sex	0.58	0.30-1.10	0.09
Baseline MoCA score	1.05	0.95-1.16	0.33
History of TIA	0.24	0.08-1.28	0.10

* All Analyses Adjusted for Age and Education

TIA = Transient Ischemic Attack

Table 9-16 Cross Sectional Univariable Analyses for Increase in DSST Score Over the 12-month Intervention Period*

Variable	OR	95% CI	P-Value
Depression			0.26
No/Mild Depression	(Referent)	(Referent)	
Moderate Depression	1.87	0.86-4.17	0.11
Severe Depression	1.49	0.39-5.64	0.55
Improved MoCA Score at End of Study	2.88	1.40-5.80	0.004
Improved DBP	0.77	0.29-1.70	0.46
Improved SBP	0.66	4.22-1.80	0.42
HbA1c Under 7% at End of Study	1.17	0.36-3.66	0.77
Feeling that I don't have a doctor who I can see regularly enough about my diabetes.	0.71	0.46-1.09	0.13
Feeling that diabetes is taking up too much of my mental and physical energy every day.	0.72	0.54-0.95	0.024
Feeling that my doctor doesn't know enough about diabetes and diabetes care.	0.99	0.97-1.02	0.94
Feeling that my doctor doesn't take my concerns seriously enough.	0.14	0.01-2.03	0.35
Rating of Health Care Provider	1.20	0.90-1.63	0.21

* All Analyses Adjusted for Age and Education

Table 9-17 Cross Sectional Multivariable Analyses for Increase in DSST Score Over the 12-month Intervention Period*

Variable	OR	95% CI	P-value
Improved MoCA Score at End of Study	2.88	1.40-5.80	0.004
Feeling that diabetes is taking up too much of my mental and physical energy every day.	0.72	0.54-0.95	0.051 ()

* All Analyses Adjusted for Age and Education

9.7 FIGURES

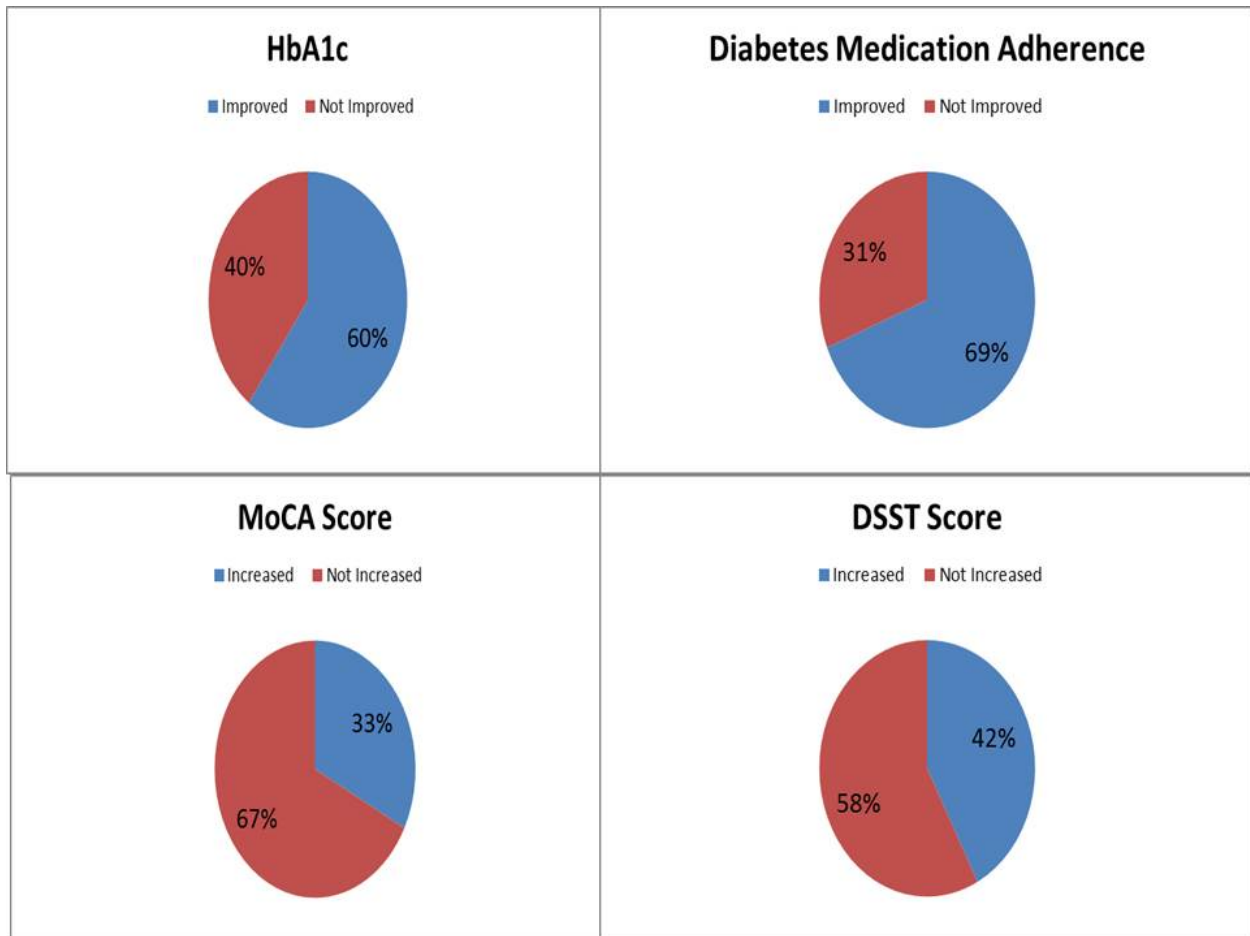


Figure 9-1 Proportion of intervention participants that achieved outcomes

10.0 DISCUSSION

10.1 SUMMARY OF STUDY FINDINGS

This dissertation examined primary and secondary outcomes from the REMEDIES 4D study, which aimed to redesign the primary care practice by placing CDEs in community-based primary care practices; following evidence-based protocols, CDEs intensified diabetes, blood pressure, and cholesterol medication therapy as well as provided diabetes self-management education to middle-aged participants with type 2 diabetes. The three specific aims of this dissertation were to: 1a) determine if improvements in clinical outcomes (HbA1c, blood pressure and LDLc) differed between those in the intervention group (i.e., who received care using the REMEDIES4D protocol) and those in the control/usual care group; ; 1b) assess differences in treatment intensification of those in the REMEDIES intervention group compared with those in the usual care group; 2a) determine if increases in clinic and medication satisfaction differed between those in the intervention group and those in the control group; 2b) determine if clinic and medication satisfaction impacted medication adherence and clinical outcomes (A1C, blood pressure, and LDLc); and 3a) among those in the intervention group, determine if increased cognitive test scores are related to improvements in diabetes medication adherence and HbA1c values; 3b) among those in the intervention group, identify predictors of improvements in

diabetes medication adherence and HbA1c values and with increased cognitive test scores at the end of the study.

For the first aim, analyses showed that patients in the intervention group had significantly lower HbA1c at the end of the study compared with those in the usual care group. However, the intervention group did not have significantly lower SBP, DBP, or LDLc values. In fact, in the multivariable model, patients in the usual care group were significantly more likely to have lower DBP at the end of the study. Even though the usual care group was more likely to have lower DBP, the mean DBP of the intervention group at the end of the study was below the goal level of 80 mmHg. Participants in the intervention group were significantly more likely to have had their diabetes medication intensified compared with patients in the usual care group, but there was not a significant difference between the two groups in the percentage of patients who had their blood pressure or cholesterol medications intensified. Both groups were equally as likely to be on an ACE or ARB throughout the study. The percentage of patients who met their HbA1c or LDLc goals was significantly increased at the end of the study but more so among those in the intervention group; at the end of the study, 1.5% of usual care participants had all four clinical values (i.e., HbA1c, LDLc, SBP, DBP) controlled whereas 11% of the participants in the intervention group had all four clinical values controlled.

For the second aim, those in the intervention group were significantly more satisfied in a number of provider and medication satisfaction areas at the end of the study, even though their satisfaction did not significantly increase between baseline and the end of the study. Clinician and medication satisfaction did appear to impact the odds of better clinical outcomes and medication adherence at the end of the study. Participants who felt respected by their providers, or rated them highly, were more likely to have better HbA1c, SBP, LDLc, anti-hypertension,

diabetes, and anti-hyperlipidemia medication adherence at the end of the study compared with participants who did not feel respected or were not satisfied with their provider. Interestingly, participants who were satisfied that their providers had enough time for them, listened to them, and explained things to them were less likely to have better clinical outcomes or medication adherence. Add a sentence about what you think of this result which was contrary to expectations. Participants who were satisfied with their medications' side effects, and with their ability to plan on when to take their anti-hypertension and anti-hyperlipidemia medications were more likely to be adherent to taking these medications, and to have lower DBP and LDLc at the end of the study. Overall satisfaction with diabetes medication reduced the odds of having lower HbA1c at the end of the study, but being satisfied in how well the medication *worked* increased the odds of having a lower HbA1c.

In the last aim, increases in cognitive test scores did not appear to be significantly associated with improved diabetes medication adherence or HbA1c. Longitudinal improvement in HbA1c was associated with higher health care provider ratings, baseline HbA1c, and testing blood glucose less than three times a day. Testing less than three times a day may be due to those who test more may have more complex disease, requiring more testing, or perhaps reporting bias. At the end of the study, increased HbA1c was associated with improved LDLc, with feeling respected by their health care provider, and with not having an improved SBP. A longitudinal improvement of diabetes medication adherence was associated with not feeling overwhelmed by the demands of living with diabetes. Similarly, at the end of the study, diabetes medication adherence was associated with high adherence to anti-hypertension medications, but no other factors. For cognitive test score increases, a longitudinal increase in the MoCA score was associated with lower distress regarding provider's knowledge of diabetes and diabetes care, no

history of angiography, and no history of hyperlipidemia. At the end of the study, an increase in MoCA score was associated with increased DSST score. While no covariate was significantly associated with a higher DSSTscore at baseline, at the end of the study, an increase in MoCA score was significantly associated with feeling that diabetes was not taking up too much mental and physical energy as well as being borderline associated with increased DSST-90 score.

10.2 CONTRIBUTION TO THE LITERATURE

The findings of this dissertation fill the gap in the research literature by analyzing various patient outcomes in the context of a CDE led intervention to improve diabetes outcomes in the primary care practice. While there are studies that examine the effect of allied health care providers managing diabetes (221; 222; 224), this is the first study where CDEs, following an evidence-based, preapproved protocol, independently provided diabetes, hypertension, and hyperlipidemia care to patients with type 2 diabetes, in a community-based, primary care setting. Previous studies were observational, did not use CDEs, or did not take place in the community (220; 222; 338) The first study in this dissertation provides evidence that when following the previously described protocols, the CDE led intervention group was more likely to have their diabetes medication intensified and to have lower HbA1c at the end of the study compared with the usual care group. The intervention group's LDLc was significantly reduced throughout the study, though there was not a significant between-group difference in LDLc at the end of the study, and there was not a significant difference in SBP between groups, illustrating that CDEs in a team-based approach can just as effectively manage these conditions. While those in the

usual care group were more likely to have lower DBP compared with those in the intervention group, the average DBP in the intervention group was below the goal level of 80 mmHg.

The second study added to the literature by illustrating which clinical and medication satisfaction areas affect medication adherence and clinical outcomes. Also, it showed that participants in the CDE-led intervention group were significantly more likely to have higher clinician satisfaction in the areas of providers ability to explain, listening, respect, addresses medical issues well, informed on patient's medical history, and overall rating, as compared with participants in the control group. Also, this study's results showed how clinician and medication satisfaction can impact medication adherence and clinical outcomes in a setting where CDEs provide care, and that the use of CDEs does not negatively affect clinical and treatment adherence outcomes in this population of adults with type 2 diabetes.

The final study added to the literature by showing that, for this group of adults with type 2 diabetes, cognitive test scores were not related to improvements in HbA1c or diabetes medication adherence. This study also examined factors that may lead to improvements in HbA1c and diabetes medication adherence in a study population receiving diabetes care from CDEs, not physicians. This study shows that diabetes distress may play an important role in improvements in HbA1c or medication adherence. This third study also examines what factors may affect increases in cognitive test scores in such a population.

10.3 STUDY LIMITATIONS

Like all studies, the studies associated with this dissertation have a number of limitations that need to be addressed. Two universal limitations are that this study population was

overwhelmingly non-Hispanic white (81%), and this study did not reach its recruitment goals. The largely white population precluded subgroup analysis on race or ethnicity. Since the recruitment goal was not reached, the power to detect certain differences was affected; while this study still had sufficient power to detect a 1% difference in HbA1c, it no longer had the power to detect the differences in blood pressure and LDLc, increasing the chance of Type II errors. Additionally in the first analysis, missing clinical data was an issue because while the CDEs were encouraged to order cholesterol and HbA1c tests for participants in the intervention group, providers caring for those in the usual care group ordered these tests at their discretion; this study had no mechanism in place to order tests for participants in the control group, thereby leading to missing data. Also, while providers in either group may order tests, it was up to the participant to follow through and have the lab work completed; this was done partly to reflect the true nature of primary care, and for future analyses investigating patient activation.

The second study also had several limitations. Due to possibility of high patient burden regarding the questionnaires, a validated medication satisfaction questionnaire was not used. Instead, a short, four-question measure for each category of medication (diabetes, anti-hypertension, anti-hyperlipidemia) was used. This measure has not been validated. Lastly, the clinician satisfaction survey that was used, the AHRQ-CAHPS Clinician & Group Survey: Diabetes Clinic Satisfaction Survey, was designed to calculate an aggregate score for individual providers, not to have each question used individually as covariates.

The greatest limitation in the last study was missing data, not at random. The usual care group could not be utilized in this study because most participants in the usual care group declined to take the cognitive tests. Unlike surveys, which could be mailed out and self-administered, the DSST and MoCA need to be administered by trained staff, due in part to

having timed components involved. The number of participants in the usual care group who completed their cognitive assessment was too small to conduct any valid statistical tests. Also, the follow up time for the REMEDIES 4D trial was only 12 months; this may be too short a time to detect any significant changes in cognitive test scores, especially in a population like ours, who did not display major decrements in cognitive function at baseline. Lastly, the outcomes in this study were dichotomous (i.e., improved score yes/no). While an improvement could be detected, the magnitude of change was not measured; without assessing the magnitude of the change in test scores over time, the clinical significance of these changes is unknown.

10.4 PUBLIC HEALTH SIGNIFICANCE

Type 2 diabetes is not only one of the most common chronic diseases in the United States, it is a one of the most common chronic diseases in the world. An estimated 29.1 million adults, ages 18 and older in the United States, have diabetes, with up to one-fourth undiagnosed, and this number is expected to rise to 48.2 million by 2050(1; 2). Diabetes was the 7th leading cause of death in the United States in 2010, with an estimated \$245 billion dollars in 2012 in both direct and indirect costs(1). Nearly 20% of healthcare dollars are spent to treat people with diabetes (13). Diabetes is a leading cause of kidney failure, blindness, and non-traumatic lower leg amputation(3; 4). People with diabetes are at higher risk of cardiovascular disease, cognitive impairment, and death than people without diabetes(5-7).

However, many diabetes-related complications can be reduced or delayed by adequate control of risk factors (e.g., HbA1c, DBP, SBP, LDLc) and by providers ensuring that their patients receive the recommended preventative care services (e.g. eye and feet exams, testing for

microalbuminuria) (12; 14; 178)American Diabetes, 2014 #168}. Currently, , people in the United States with diabetes do not have their clinical risk factors adequately controlled, partially due to lack of medication intensification, and there are many missed opportunities for patients to receive needed preventive services(4; 189). Missing these opportunities to perform needed services and intensify medication is called clinical inertia (185; 186). By using CDEs to deliver medication therapy, order preventative services, and provide education regarding diabetes self-care and disease management strategies, this study aimed to reduce clinical inertia and ensure better control of patients' clinical values.

CDEs are highly-educated but are underutilized in the primary care setting. Study results illustrate that redesigning the primary care practice, with an increased utilization of CDEs, can effectively treat and improve diabetes patients' clinical values. Indeed, as shown in the first study, the intervention group had an overall reduction of 1.1% in HbA1c. Previous research shows that a 1% reduction in HbA1c decreases the relative risk for microvascular complications by 37%, for diabetes-related deaths by 21%, and for myocardial infarction by 14% ((11); (12)), Adding CDEs to primary care practices and allowing them to help treat diabetes patients, following evidence-based, preapproved guidelines, should correlate with better diabetes management and better glycemic control. This, in turn, should reduce the risk and severity of diabetes-related complications, with lower associated personal and public health care costs. . Lower rates of complications will lead to improved quality of life for people with diabetes and for many, may even extend their life.

10.5 FUTURE RESEARCH

There are a number of future research directions that can be pursued as a result of this research. First, investigators should replicate this study in a larger, more diverse population. Not only would this make the findings more generalizable, it would allow for sub-group analyses, and improve the ability to detect between-group differences in LDLc and blood pressure. Also, a larger study may provide even more evidence to spur a redesign of the primary care system in regards to diabetes and CDEs.

Much of the provider satisfaction literature concentrates on testing a patient's health literacy and knowledge. Since this was not done measured in the current study, it would be interesting to see if there was a significant difference in patients' health literacy and knowledge, or perceived health literacy and knowledge, in the two study groups. This measure could also help analyze the impact that health literacy and knowledge has on provider satisfaction, medication adherence, and health outcomes. A replicated study could also be altered so that it would increase the researcher's probability of having an adequate sample of participants with data on cognitive measures, or include a more comprehensive cognitive test battery to analyze domain-specific effects on diabetes control measures. This would allow researchers to see if there were any significant differences between groups, and if so, how it may affect the outcomes of interest. Additionally, if the research study was longer (i.e., more than one year) and incorporated repeated cognitive testing, it could allow more time points so as to better measure any changes in cognitive scores throughout the study.

Further research in this area has the opportunity to strengthen the case for allied health care providers in the primary care practice, which can help improve the quality of life and reduce the number of complications of those with diabetes.

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