

2014

## EVALUATING THE ROLE OF HYPOGLYCEMIA & COMORBID ILLNESS ON DIABETES MANAGEMENT BEHAVIORS

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EVALUATING THE ROLE OF HYPOGLYCEMIA & COMORBID ILLNESS ON DIABETES  
MANAGEMENT BEHAVIORS

BY

SAUMITRA VIJAY REGE

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE  
REQUIREMENTS FOR THE DEGREE OF  
DOCTOR OF PHILOSOPHY  
IN  
PHARMACEUTICAL SCIENCES

UNIVERSITY OF RHODE ISLAND

2014

DOCTOR OF PHILOSOPHY

OF

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2014

## **ABSTRACT**

Over the recent years, the incidence of diabetes has significantly increased. Use of preventive services and treatment with oral antidiabetic drugs (OAD) has remained cornerstone in the management of type 2 diabetes (T2DM). Despite strong evidence that treating diabetes using these disease management strategies decreases morbidity, mortality and complications, glycemic control as well as other diabetes related outcomes remain unsatisfactory. The prevalence of diabetes in the United States has grown vastly in proportion over the last few years with the American Diabets Association estimating that 9.3% of the population suffered from diabetes in the year 2012. These estimates are expected to increase in the future with the World Health Organization (WHO) estimating that 366 billion people (4.4%) will have diabetes. Diabetes places a greater clinical as well as economic burden on the patients as well as the health care system.

The presence of comorbid depression is frequent in people suffering from diabetes and can cause health outcomes in patients with diabetes. Poor adherence and persistence to diabetic medications resulting from the occurrence of adverse events is a cause of poor health as well as economic outcomes. There is a continuing need to evaluate the associations between comorbidities as well as common complications of medication treatment in persons with diabetes and examine how they influence health behavior. Evidence regarding differences in the utilization of preventive care services in diabetic patients with and without comorbid depression is scant. Similarly, the factors that predispose an individual to hypoglycemia as well as

the association between hypoglycemic episodes and persistence to OAD therapy, specifically sulfonylureas, has rarely been quantified retrospectively. This dissertation utilizes the manuscript format and has four fold objectives:

1. To review the current literature regarding the role of hypoglycemia and comorbid depression in the diabetes and examine their impact on clinical and economic aspects of diabetes management;
2. To quantify the effect of comorbid depression on the rates of preventive care service use in a nationally representative population of US adults;
3. To identify significant predictors and estimate the costs associated with the occurrence of hypoglycemia in the inpatient and outpatient settings.
4. To evaluate the association between the development of hypoglycemia and persistence to oral sulfonylurea therapy in patients newly initiated on this class of OAD medications.

In order to review the literature regarding the effect of hypoglycemia and comorbid depression and diabetes, we utilized various biomedical and psychological databases. We analyzed the effect of comorbid depression as a principal risk factor associated with use of ADA recommended preventive services in patients with diabetes using the Medical Expenditure Panels Survey Data. A logistic regression was performed to achieve this objective and all the relevant confounders were controlled for in order to achieve the results. Claims data provided by the Blue Cross and Blue Shield of Rhode Island was utilized to assess the relationship between hypoglycemia and persistence to sulfonylurea medication as well as outline the predictors and costs of

hypoglycemia. A time-varying Cox proportional hazards regression model was utilized to compare the hazard rate of medication discontinuation in diabetic patients that were exposed to hypoglycemic events, compared to those that were unexposed. A predictive modelling approach was utilized to highlight the factors associated with hypoglycemia.

While the impact of comorbid depression and diabetes was significant both clinically and economically, it was seen that the extent of preventive care service use was comparable for diabetic patients with and without comorbid depression but suboptimal in general thus indicating major gaps in the implementation of ADA recommended preventive care practices. While depression was not significantly associated with increased use of the recommended diabetes preventive care services, other sociodemographic factors were seen to contribute. Moreover, though no significant association between events of hypoglycemia and subsequent discontinuation sulfonylurea medication was illustrated, we demonstrated several clinical factors to have a profound impact on the risk of developing hypoglycemic episodes.

## **ACKNOWLEDGMENTS**

. The completion of this thesis has made possible with the care, support, and encouragement of numerous people including my family, instructors, friends and colleagues. At the end of this journey, I would like to thank all people who made this thesis a possible and an unforgettable experience for me.

First of all, I would like to thank my advisor, Dr. Brian Quilliam for his unconditional guidance, support, patience and encouragement. He has always been like a guardian as well as a constant source of inspiration and I will always remain thankful for having such a knowledgeable mentor and exceptional human being as my major advisor. I will always be indebted to him for providing me with the opportunity to learn from him, which has helped me build a strong platform for my future endeavors. He will always retain a very special place in my life and I look forward to this association growing stronger in the future. I may not have been able to reach where I am today without his invaluable presence.

I take this opportunity to sincerely acknowledge all people at the University of Rhode Island who have become an important part of my life in the past few years. I will always remain eternally obliged to Dr. Celia Macdonnell for being a support system over all these years. Working for her has been one of the best experiences of my student life. She has been a guiding light over all these years, preparing me for the future and treating me like family. Dr. Paul Larrat has been one of the most wonderful people I have met and I have always enjoyed speaking to him on various

topics. I am grateful to Dr. Cynthia Willey for all her inputs, suggestions and attention which has helped me immensely to grow academically ever since I first attended her classes. Dr. Stephen Kogut has been one of the most welcoming and helpful people to me. He has always been approachable whenever I have needed any advice. He has taken keen interest in my development as a PhD candidate and I truly appreciate that. I am highly obliged to have been able to work with Professor Rita Marcoux. She has been a pillar of strength for me over all these years. Apart from wonderful academic experiences as a TA, her support and care has been immense and unwavering. I would also like to say a heartfelt thank you to Barbara Ray, my supervisor for the safety work I have been doing over the years. I will always remember her generosity and concern for me ever since my first days here at URI. I would also like to thank Mr. Chuck Wentworth for his valuable suggestions and motivation during my work with the claims based data. Without their support and input and personal cheering, it would have not been possible for me to complete my degree. I will always remain eternally grateful to this select group of people.

My gratitude is also extended to members of my dissertation committee, Dr. Rachel DiCioccio and Dr. Anne Seitsinger. They have been extremely kind and helpful to take time out of their busy schedules and attend my defense.

My acknowledgements would surely not be complete without thanking my parents and family. My parents Mr. Vijay Rege & Mrs. Anuradha Rege, and my brother Mr. Ram Rege, have worked tremendously hard and made many sacrifices to give me a good foundation to build a future. They have instilled values of hard work,



self-respect and resilience in me. Words will not be enough to express how much I owe them for having faith in me, supporting me and, more importantly, loving me through good and bad times. Without their support, this would not have been possible. I would like to specially mention my aunt Dr. Vidya Rege David, who made it possible for me to reach this far. She never let me miss my parents for a moment in the past 7 years and I will always cherish her love, support, and care over all these years. I would also like to thank my brother and role model Dr. Bhagwant Rege for always being there whenever I have needed him as a friend, philosopher, and guide. I will never forget my first few months in the United States and how difficult it would have been without having him around. I am also grateful to my friends, Dr. Shripad Chitnis, Mr. Chinmay Deshpande, Dr. Rahul Kadam, Mr. Rohan Tarabadkar, Dr. Vipin Jain, Mrs. Anshu Jain, Dr. Satyakam Patnaik and Ms. Harini Chinthapatla. More than being friends, they have been a family and have been a treasured part of my life as a graduate student. The precious memories I have with them will always have a special part in my heart.

My fellow graduate students' support has been continuous source of encouragement during my long journey in finishing this doctoral program. Particularly, I would like to thank my department mates and friends Yizhou Ye and Ajinkya Pawar for keeping me company and creating a wonderful environment to work in.

Last, but certainly not least, I would like to thank Ms. Shalini Singh for her unconditional love, patience, support and unwavering belief in me. We have grown

together in this journey of 9 years from being fellow pharmacy students in India to the completion of this program. Without her support and sacrifice, all these years would have surely been much harder. No words can express my appreciation for all she has done. She has helped me in being a better human being and I hope to live up to her expectations in the future. I have been incredibly lucky to have her by my side as I have lived my dream of being in the United States.

## Dedication

I would like to dedicate my dissertation work to my family, especially my parents Vijay and Anuradha Rege, my brother Dada, my late grandmother Kamala Bai Rege, my grand parents Manohar and Indumati Nadkarni, my aunt Jaya Mavshi as well as Shalini Singh, who have all loved me endlessly and have been on my side all these years.

## **PREFACE**

To the reader: This dissertation utilizes the manuscript format, and is composed of four chapters relating to the evaluation of the role of hypoglycemia & comorbid illness on diabetes management behaviors

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## Manuscript 1

### **Role of Hypoglycemia & Comorbid Illness on Diabetes Management: A Review**

Publication status: In progress, planning on submitting to the Journal of American College of Clinical Pharmacy

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Short Title: Association between Adherence and Hypoglycemia

Word length: 4,521 References: 111 Tables: 0 Figures: 0

Short Title Manuscript I: Diabetes Management Review.

## *1.1 Diabetes*

Diabetes is a chronic metabolic disorder of characterized by different pathways. It results in hyperglycemia with an abnormality in the body's capability to convert glucose (sugar) to energy. Type 2 diabetes (T2DM) is the most frequent subtype of diabetes since it accounts for up to 90% of all cases of diabetes worldwide.<sup>1</sup> Diabetes is the seventh leading cause of death in the United States.<sup>2,3</sup> Diabetes is the most significant cause of macrovascular and microvascular complications.<sup>4,5</sup> Patients with diabetes have a lower quality of life as compared to people of the same age group without diabetes and it is even lower in cases of diabetes complications and disease progression.<sup>6-8</sup>

Recent estimates put the prevalence of diabetes for individuals aged 20 to 74 worldwide at 6.4% in 2010, and it is estimated that the prevalence would increase to 7.7% (439 million patients) by the year 2030.<sup>9</sup> It is one of the most prevalent, debilitating, and costly chronic conditions, both nationally as well as globally, resulting in substantial mortality, morbidity, and economic burden.<sup>4,5,10</sup> During the last 20 years, the prevalence of diabetes has increased dramatically in many parts of the world and the disease is now a worldwide public health problem. The World Health Organization estimates that the total number of people with diabetes is projected to rise from 171 million in 2000 to 366 million in 2030.<sup>11</sup> According to the American Diabetes Association (ADA), the prevalence of diabetes in the United States was about 9.3% in the year 2012 with 29.1 million people diagnosed with this

disorder according to the Centers for Disease Control (CDC), which was significantly higher than the 25.8 million (8.3%) reported in previous years.<sup>12,13</sup> In addition to this, another 7 million people are estimated to be suffering from undiagnosed diabetes and 86 million are estimated to suffer from prediabetes.<sup>14</sup> The CDC estimates that among U.S. residents aged 65 years and older, 10.9 million, or 26.9%, had diabetes in 2010.<sup>15</sup> This number is projected to rise rapidly with the ageing of the population and the corresponding increase in the prevalence of chronic conditions.<sup>2,16,17</sup> Danaei et al. in a study to estimate the undiagnosed diabetes prevalence as a function of a set of health system and sociodemographic variables, found that prevalence of diabetes in the U.S. was 13.7% among men and 11.7% among women  $\geq 30$  years.<sup>18</sup> Previous studies have noted major cultural and racial variations in the prevalence of T2DM.<sup>13,19,20</sup> According to the ADA, 12.6% non-Hispanic blacks have T2DM compared to 7.1% non-Hispanic whites in the United States, with the highest prevalence of diabetes found in the southern states.<sup>13,21</sup>

In a recent study by the ADA to estimate the total economic cost of diabetes for the United States, it was demonstrated that in the year 2007 the economic burden was estimated to be \$174, approximately 1 of 8 dollars spent on medical care, as compared with \$98 billion in 1997.<sup>10,22,23</sup> In the same year, the approximate total cost for treating diabetes was \$232 billion. Moreover, the total costs of diabetes had increased to \$245 billion with \$176 billion attributable to direct medical costs and \$69 billion to lost productivity.<sup>10</sup> After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes

were 2.3 times higher than those in the absence of diabetes.<sup>10</sup> Literature suggests that a high degree of health care resource use can be attributed to diabetes namely hospital inpatient days (25.7%), nursing/residential facility days (33.3%), prescription medications, and visits to the physician, emergency room, hospital outpatient etc. Previous research suggests that these estimates are higher in cases of uncontrolled diabetes and diabetes with complications.<sup>10</sup>

The increasing prevalence of the disease and thereby its economic as well as social impact emphasizes the importance of effective diabetes prevention and care.

## *1.2 Use of Preventive Services in Diabetes*

Apart from being a major cause of heart disease and stroke, diabetes poses an increased risk of cardiovascular, peripheral arterial and cerebrovascular diseases.<sup>24-26</sup> Previous studies also note a much higher proportion of non-traumatic lower limb amputations, kidney failure and blindness in diabetic patients.<sup>26</sup> A number of studies have concluded that timely utilization of medical and preventive care is an ideal practice for the management of diabetes.<sup>27,28</sup> These services can be vital in the incidence and progression of any diabetes specific complications.<sup>29</sup> Controlling blood glucose, blood pressure, and LDL cholesterol levels can reduce the microvascular complications like eye, kidney, and nerve diseases as well as macrovascular complications like heart attack, stroke, and lower-extremity amputations. For example, Litzeman et al. in a blinded, randomized, controlled trial of patients in an academic general medicine practice setting found that better foot care in patients with diabetes were likely to have reduced prevalence of lower extremity clinical disease.<sup>28</sup> One of the principal preventive services in patients with diabetes is the testing the A1C which might demonstrate the patient's blood glucose levels. Similarly, routine eye exams diagnose symptoms of diabetes related eye disease and this early detection is usually instrumental in preventing the progression this disease. Comprehensive foot care programs include assessment and treatment of feet of the diabetes patient and can help reduce amputation rates. Other preventive tests include timely immunization against pneumococcal disease and influenza as well as regular blood pressure and medical checks.



### *1.3 Depression*

Major depressive disorder (MDD) is a grave and recurrent condition affecting around 121 million people worldwide. The World Health Organization (WHO) recognizes depression as the fourth leading cause of disease burden associated with non-fatal health outcomes and a leading cause of disability around the world.<sup>30</sup> It has been widely reported in the literature that depression is often underdiagnosed and under treated.<sup>30,31</sup> Even though the scenario with respect to treatment rates has been positively changing in the past decade, many patients still suffer from symptoms of depression.<sup>32</sup> Gonzalez et al. in a study of a large national sample found that majority of the people suffering from depression did not get the guideline recommended degree of care and large disparities existed based on various factors like race and ethnicity.<sup>33</sup>

Kessler et al. in a study using the National Comorbidity Survey Replication (NCSR) suggested that in the United States, the lifetime prevalence of depression was 16.2% and the 12-month prevalence was 6.6%.<sup>32</sup> Bromet and colleagues, in a study conducted in over 18 countries reported that the average lifetime prevalence of depression was 14.6% in high-income countries and 11.1% in middle to low income countries.<sup>34</sup> Mathers et al. in a study projecting mortality and burden of disease by cause to year 2030 found that depression was predicted to hold the second position among diseases contributing to the global burden of diseases by 2030 , and there has

been a 37% increase in disability-adjusted life years of depression from the year 1990 to 2010.<sup>35</sup>

Evidence from studies suggests apart from being a major cause of morbidity, mortality and disability, MDD is responsible for higher economic costs by means of health care resource use as well as indirect costs including workplace absenteeism, diminished, or lost work productivity and increased use of healthcare resources.<sup>6,36-38</sup>

This economic burden of depression has been evaluated in several studies nationally as well as worldwide. For example, Greenberg et al. estimated the burden of depression in the United States to be \$104 billion divided as \$33 billion (31%) in medical care; \$6 billion (7%) in mortality due to suicide; and \$65 billion (62%) in workplace productivity losses.<sup>39</sup> It has also been noted that the costs of depression

increased from \$77.4 billion in the year 2000 to \$83.1 billion in the year 2010.<sup>40</sup>

Similarly, Lupa et al. in a systematic review of cost of illness studies of depression estimated that the average annual costs per case ranged from \$1000 to \$2500 for direct costs, from \$2000 to \$3700 for morbidity costs and from \$200 to \$400 for mortality costs.<sup>41</sup> Working people with depression have a lower degree of

productivity in terms of higher rates of absenteeism and reduced on-the-job output and can lead to disability.<sup>42-44</sup> Greenberg et al. noted that lost productivity accounted

for more than 60% of the total social economic burden of depression in the US in 2000, which was estimated at \$52.9 billion.<sup>39</sup> Stewart et al. in a study of employed

individuals, who participated in the American Productivity Audit, reported that people with depression lost 5.6 hours of productive work every week.<sup>45</sup> Pratt et al.

examined data from Data from the National Health and Nutrition Examination Survey (NHANES) and concluded that 80% of people with depression reported some level of functional impairment because of their depression, and 27% reported serious difficulties in work and home life.<sup>44</sup>

#### *1.4 Comorbidity of Diabetes and Depression*

A large body of literature has highlighted the association between diabetes and depression.<sup>46-48</sup> The essential finding in the aforementioned analyses has been that that diabetes and depression co-occur frequently with the presence of one condition significantly increasing the likelihood of patient suffering from the other.<sup>48,49</sup> A systematic review by Roy and colleagues suggested that prognosis of comorbid depression in patients with diabetes, in terms of its clinical and societal implications, is worse for either condition in comparison to when they occur individually.<sup>50</sup>

##### *1.4.1 A Bi-Directional Relationship between Diabetes and Depression*

In a review of literature Egede et al. noted that previous research indicated a complex relationship between diabetes and depression because the temporality of this association is not clear.<sup>6</sup> There is a growing body of evidence, which suggests that there exists a bidirectional relationship between these two chronic disorders.<sup>51</sup> Moreover, several physiological and behavioral mechanisms have been studied to explain this possible link between diabetes and depression. Mezuk et al. in a meta-analysis of studies from 1950 to 2007 of diabetes and depression, established that people with depression had a 60% increased risk of developing diabetes compared to non-depressed patients while people with diabetes had a 15% increased risk of developing depression compared to non-diabetics.<sup>52</sup> Pan et al. studied women over a 10 year period and found that the relative risk for T2DM in women with depressed

mood was higher as compared to those who were non depressed (OR 1.17; 95% CI 1.05–1.30).<sup>53</sup> Studies have found incidence of depression as a modifiable independent risk factor in the onset of diabetes.<sup>54-56</sup> Golden et al. performed a longitudinal study depressive symptoms at baseline were associated with an increased incidence of T2DM at follow-up over a 3-year period; an increased risk for developing depressive symptoms over the 3-year period was associated with treated T2DM, but conversely baseline impaired fasting glucose and untreated T2DM were associated with reduced risk for depression.<sup>51</sup> The increased risk of developing diabetes might be due to the negative physiologic effects of depression on glucose metabolism as well as neuroendocrine and autonomic nervous systems.<sup>54</sup> Similarly, diabetes can also act as a precursor to depression through various clinical and psychological mechanisms.<sup>50</sup> Poor metabolic control and increasing complications as a result of diabetes may result in or further worsen depression and lessen response to antidepressant treatment.<sup>6,50</sup> For example In a study of 1,586 older adults from the Rancho Bernardo study, Palinkas et al. reported that there was a 3.7- fold increase in odds of depression in those with a prior diagnosis of diabetes.<sup>57</sup> Thus, as suggested in a recent meta-analysis, there is lack of concrete information supporting the direction of relationship between diabetes and depression with there being clinical and epidemiological support for both hypotheses.<sup>58</sup>

#### *1.4.2 Prevalence of Depression in Diabetes*

It is well documented that depression is significantly higher in patients with diabetes as compared to the general population.<sup>48,59</sup> Anderson et al. and Egede et al. found that the odds of suffering from depression among patients with diabetes are two fold as compared to the patients without diabetes.<sup>47,49</sup> Ali et al. in a systematic literature review in order to estimate the prevalence of clinically relevant depression in adults with T2DM had similar results with odds of suffering from comorbid depression being nearly twice among diabetic patients (OR = 1.6, 95% CI 1.5–1.7).<sup>48,60</sup> These findings of diabetic population being more likely to suffer from depression have been reaffirmed by World Mental Health Surveys, which indicate an elevated risk of mood (OR=1.38) and anxiety disorders (OR=1.20) in patients with diabetes compared with persons without diabetes.<sup>60</sup> The reported prevalence of depression in patients with diabetes varies widely due to an array of factors but most studies estimate that 10 -30% of individuals with diabetes suffer from various forms comorbid depression with some studies indicating that the rates may be as high as 39%.<sup>47,49,61,62</sup> Li et al. examined data from the 2006 Behavioral Risk Factor Surveillance System (BRFSS), a standardized telephone survey of U.S. adults aged 18 and older and found that the age adjusted rate of depression was 8.3%.<sup>63</sup> In a second study by the same authors investigating the prevalence of undiagnosed depression among individuals with diabetes found the adjusted and unadjusted prevalence of undiagnosed depression to be 8.7% and 9.2%, respectively.<sup>64</sup> Maraldi and colleagues, in a secondary analysis from the Health ABC study, a prospective cohort (n=3,075) of community-dwelling

adults who are aged between 70 and 79 years, found an increased risk of depressed mood among people with diabetes.<sup>65</sup> D Groot et al. found that the lifetime prevalence rates of major depression among patients with diabetes to range from 14.4% to 39% which are approximately three times higher than the rates in general population.<sup>66</sup> A population-based epidemiologic study conducted to determine the behavioral and clinical characteristics of diabetes associated with depression found that 501 of 4,193 study participants (12%) met Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV), criteria for MDD and 357 participants (8.5%) met criteria for minor depression (10-7,8).<sup>67</sup> Ali et al. also found that the prevalence of depression was significantly higher among patients with T2DM (17.6%) than those without diabetes (9.8%).<sup>48</sup>

#### *1.4.3 Clinical Implications Of Comorbid Diabetes And Depression*

The clinical implications of occurrence of comorbid depression in patients with diabetes are of serious concern since it is associated with poorer diabetes outcomes.<sup>48,68</sup> Apart from having a negative impact on the physical, mental and social wellbeing of the diabetic patients, it might also have implication on quality of life, rates of mortality and morbidity.<sup>49</sup> Studies have shown that depression is associated with a higher number of diabetes complications and can exacerbate the severity of these complications.<sup>50,52,54,69</sup> A meta-analysis by De Groot and colleagues demonstrated a clinically significant relation between depression and several diabetic complications like retinopathy, nephropathy, neuropathy, sexual dysfunction, and

macrovascular complications.<sup>66</sup> Lustman et al. found that depressive symptoms in patients are associated with decreased glycemic control.<sup>70</sup> Richardson et al. assessed the longitudinal effects of comorbid depression on glycemic control and observed that depression was associated with persistently higher A1C levels over the time period.<sup>71</sup> Moreover, Katon et al. in a study of 4,225 patients from nine primary care clinics of a nonprofit health maintenance organization found that patients with MDD and diabetes, with or without evidence of cardiovascular disease, were 1.5 to 2 times as likely as nondepressed patients with diabetes to have  $\geq 3$  cardiac risk factors.<sup>72</sup> In another study of 10,704 Medicare beneficiaries in the U.S, Katon et al. reported that beneficiaries with diabetes and comorbid depression had a 36–38% increased risk for all-cause mortality over a 2-year period.<sup>73</sup> In a study of 10,025 patients from the NHANES I Epidemiologic Follow-up Study, Egede et al. found that hazard rates for all-cause mortality for individuals who had diabetes and depression were 2.50 (95% CI 2.04–3.08) compared with those without diabetes or depression and concluded that comorbid depression is associated with a significantly higher risk of death.<sup>74</sup>

#### *1.4.4 Quality Of Life In Patients With Diabetes And Comorbid Depression*

In addition, it is increasingly evidenced in the literature that presence of comorbid depression in diabetes is significantly associated with deterioration of various quality-of-life indices such as physical, mental, and social functioning.<sup>75-77</sup> For example, in a study investigating the effects of depression on the quality of life in type II DM patients with and without current major depressive episode diagnosed according to



DSM-IV criteria, Eren et al. found a significant decline in quality of life in individuals with comorbid depression and diabetes.<sup>78</sup> Various instruments have been used in studies which have proved treatments and complications in patients with comorbid depression and diabetes adversely affect the quality of life of these patients.<sup>76</sup>

#### *1.4.5 Health Care Resource Use In Patients With Diabetes And Comorbid Depression*

Previous studies evaluating health care expenditures and utilization have found comorbid depression and diabetes are associated with higher direct and indirect health care costs due to greater use of resources, lost work time and disability.<sup>49,79-</sup>

<sup>81</sup> Simon et al. in a study assessing the relative contributions of diabetes complications, depression and comorbid medical disorders to health service costs in adults with diabetes, found that the health care costs were 70% higher in individuals with comorbid depression and diabetes.<sup>82</sup> Analyzing a nationally representative survey in the United Kingdom, Das-Munshi et al. found an increased use of health care resources among diabetic patients with depression in the form of higher frequency of hospital admissions and physician visits.<sup>83</sup> Finkelstein et al. found that treatment of depression was associated with greater use of inpatient and outpatient medical services.<sup>81</sup> Himelhoch et al. found that a diagnosis of depression was associated with greater use of acute care services (emergency department and inpatient care) among Medicare beneficiaries with diabetes and other chronic medical conditions.<sup>84</sup> Using Medical Expenditure Panel Survey (MEPS) data, Egede et al. found that self-reported history of depression was associated with higher total

health service costs (\$247,000,000 vs. \$55,000,000, P value < 0.0001) among respondents with diabetes.<sup>49</sup> In a sample of 367 health maintenance organization members with diabetes, Ciechanowski et al. found that higher Hopkins Symptom Checklist depression scores were associated with significantly higher health service costs, with severe depression accounting for up to 86% higher costs.<sup>80</sup> In a study of 55,972 adults with diabetes, Le et al. found that patient with diabetes and depression had higher diabetes-related medical costs (\$3,264) than patients with diabetes alone (\$1,297). They also found that depressed patients with diabetes had higher total medical costs (\$19,298) than patients without depression (\$4,819).<sup>6</sup> Egede et al. found that adults with diabetes and depression were more likely to miss more than 7 workdays in any given year.<sup>85</sup>

#### *1.4.6 Self Care Behaviors In Patients With Diabetes And Comorbid Depression*

Self-care behaviors are of highly critical in the management of diabetes since patients with comorbid depression and diabetes are at a higher risk for worse health outcomes as compared to individuals with a single disorder.<sup>86</sup> Clinical management guidelines stress the importance of self-care behaviors in diabetes including adherence to dietary recommendations, diabetic knowledge, adequate physical activity and exercise, smoking cessation, adherence to prescribed medication and other therapies and timely monitoring of blood glucose.<sup>55</sup> Previous research indicates that patients with comorbid depression and diabetes have lower rates of adherence to these patient initiated components of diabetes care.<sup>66,87</sup> For example, in a study

examining the impact of depression on adherence to oral hypoglycemic agents (OHAs) of patients identified from a Medicaid claims database using Medication Possession Ratio (MPR), Kalsekar et al. indicated that patients with depression had 3-6% lower adherence to OHAs compared with patients without depression.<sup>88</sup> There is also evidence to suggest lower adherence rates to other medication regimens as a result of co-existing depression in diabetes.<sup>55</sup> Apart from non-adherence to medications, higher body mass index (BMI) and tobacco use are concerning aspects of poor self-care behaviors since they might cause insulin resistance and increased morbidity in patients with diabetes.<sup>67</sup> Gonzalez et al. in a study examining the relationship between comorbid depression and diabetes self-care behaviors noted that controlling for relevant covariates, patients with comorbid depression and diabetes reported significantly fewer rates of adherence to a full range of self-care behaviors along with a 2.3-fold increase in the likelihood of missing medication doses.<sup>89</sup>

### *1.5 Oral Hypoglycemic Agents And Goals Of Therapy*

Previous research has identified some of the principal goals of oral antidiabetic therapy. ADA proposes a glycated hemoglobin (A1C) level of less than 7% and preprandial blood glucose level of 80–120 mg/dL, a bedtime blood glucose level of 100–140 mg/dL.<sup>90,91</sup>

Garber et al. and Grant et al. have demonstrated that oral hypoglycemic agents (OHAs) were effective in lowering A1C by 1–2%.<sup>92,93</sup> Achieving lower A1C levels has demonstrated a significant beneficial impact on reducing diabetes related micro and macro vascular complications including retinopathy, nephropathy and neuropathy.<sup>94</sup>  
<sup>97</sup> Results of the U.K. Prospective Diabetes Study (UKPDS) suggested that for every percentage-point reduction in A1C, it is possible to achieve a 22% to 35% reduction in microvascular complications.<sup>97,98</sup> However, previous literature does not clearly define the advantages of intensive therapy to achieve lower A1C levels while reducing macrovascular and microvascular complications.<sup>99</sup> With these goals in mind, the selection of a particular agent is based on factors such as clinical and biochemical characteristics of patient, safety concerns, severity of diabetes as well as the available therapeutic options. Recent advances in research have presented clinicians with a plethora of oral medications which are effective in controlling hyperglycemia associated with T2DM as well as managing diabetic complications, thus making the decision making process complex. Moreover, most of the patients require 2 or more medications to achieve the desired glycemic control over a period of time.<sup>100</sup> In 2011,

there were 8 classes of oral medications approved by the FDA for treating T2DM such as – biguanides, sulfonylureas, meglitinides, thiazolidinediones (glitazones), alpha-glucosidase inhibitors, DPP-4 inhibitors, bile acid sequestrants, dopamine-2 agonists<sup>91,101</sup>. Mann et al. using a series of cross sectional surveys, reported that the proportion of US adults who took 2 classes of medications was 35% with an increase of 6% to 14% in the number of patients who took 3 or more classes of medication.<sup>102</sup>

### *1.6 Hypoglycemia in T2DM*

Hypoglycemia is one of the most common as well as dangerous side effects of T2DM therapy. Even though it is well proven in evidence that tighter glycaemic control may be instrumental in reducing the risk of other serious complications of T2DM like retinopathy, neuropathy, and nephropathy, it can also present an additional risk of severe hypoglycemia. In many T2DM patients, hypoglycemia is responsible for recurrent morbidity and at times, can be a cause of mortality thereby creating a barrier to the long term benefits of optimal glycaemic control.<sup>103</sup> Cryer et al. in a comprehensive review of literature mentioned that though there is no concrete evidence with respect to the frequency of hypoglycaemic episodes in T2DM patients, the rates of severe episodes requiring medical attention in patients on intensive insulin therapy varied from 3 to 73 episodes per 100 patient-years, which was about 10% of those in Type 1 Diabetes.<sup>103-105</sup> The United Kingdom Prospective Database Study (UKPDS) reported that 2.4% of patients using metformin, 3.3% of patients using a sulfonylurea, and 11.2% of patients using insulin reported incidents of severe hypoglycemia requiring medical attention over the 6 years of follow up period with hypoglycemia becoming a limiting factor to glycaemic control over a period of time.<sup>106</sup>

### *1.7 Persistence to OADs in T2DM*

Medication persistence or conforming to the recommendation of continuing treatment for the prescribed length of time is an important issue in the long term management diabetes considering the chronic nature of the disease and the nature of the treatment regimen intended to achieve the desired glycemic targets.<sup>107</sup>

Cramer et al. in a review of literature to determine the extent to which patients fail to comply with the doses of medications prescribed for diabetes noted that the rates for treatment persistence ranged from 16 to 80% when the patients continued taking their medications for at least 6-24 months. The authors noted that the methodologies followed by the researchers varied in that the cross-overs to an alternative OHA or insulin might not have been counted as discontinuation.<sup>108</sup>

Bocuzzi et al. conducted a retrospective analysis of a large administrative pharmacy claims database, using data on continuously pharmacy benefit-eligible members prescribed OHAs, reported that the 12-month persistence rate for the OHA cohort was low, ranging from 31% for alpha-glucosidase inhibitors to 60% for metformin.<sup>109</sup>

Guénette et al. studied the 1-year treatment persistence and compliance of new oral antidiabetic drug (OAD) users and found that 79.3% of the cohort members persisted with the therapy during their first year of antidiabetic treatment.<sup>110</sup>

In another literature review, Cramer et al. reported that 45% of the individuals who newly initiated oral antidiabetic therapy were non adherent to the regimen and almost 33% of the patients discontinued their therapies in 12 months.<sup>108</sup> Other past studies have reported persistence estimates for oral antidiabetic medications from a low of 15%

to a high of 76% with the variations attributed to differences in methodologies, definitions of persistence as well as length of the follow up periods. Non-persistence with therapy most often leads to failure in meeting glycemic goal thus leading to avoidable undesirable adverse health outcomes.<sup>111</sup>



### *1.8 Conclusions*

It is clear from the above literature review that issues with diabetes management are highly prevalent and are significantly associated with negative health and economic outcomes. The coexistence of diabetes and depression also results in compromised self-care behaviors which are essential in the management of both the diseases especially diabetes. Of greater importance among the self-care behaviors is the suboptimal utilization of preventive care services since these are particularly essential in preventing the complications in diabetes. Similarly, medication persistence and hypoglycemia are issues affecting the achievement of desired glycemic goals. There is a need to develop strategies to address both patient and other health care related factors in order to increase the potential effectiveness of disease management in diabetes. A multifactorial approach might be essential to counter the adverse health effects of comorbid diseases as well as adverse effects of diabetic medications in patients with diabetes.

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## Manuscript 2

### **The Effect Of Comorbid Depression On The Use Of Preventive Care Services In Patients With Diabetes**

Publication status: In progress, planning on submitting to the Diabetes Care Journal

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Short Title: Association between Adherence and Hypoglycemia

Word length: 8,456 References: 66 Tables: 6 Figures: 3

Short Title Manuscript II: Depression And Use Of Diabetes Preventive Services.

## *2.1 Background and Significance*

The American Diabetes Association (ADA) publishes Clinical practice guidelines for persons with diabetes annually. These guidelines are evidenced based and are intended to improve the quality of care for patients with diabetes.<sup>112</sup> Evidence from previous research has been instrumental in the development of several clinical practice guidelines that are intended to improve the quality of care for diabetes patients<sup>112</sup>. These recommendations suggests that adherence to these recommended guidelines is likely to have a positive impact on the morbidity and mortality related to diabetes thereby reducing the clinical as well as economic burden of diabetes as well as improving the management of diabetes.<sup>12,27,28,113,114</sup>

Despite this knowledge, the use of the clinical preventive services in the U.S. adult population is suboptimal and is quite variable.<sup>115</sup> For example, The Healthy People 2020 initiative, reported low levels of use of multiple clinical preventive services for diabetes as well as other diseases.<sup>116</sup> Previous research suggests the use of preventative services ranges from 10% to 85%, depending on the particular service.<sup>117</sup> Evidence from population-based studies in various settings also indicates that there is a significant difference between reported levels of use of preventive care practices among people with diabetes and the degree of recommended use for optimal level of care.<sup>118</sup> This discrepancy might be primarily attributed to the effects of race/ethnicity, income, health insurance coverage, and comorbidities.<sup>119-121</sup> For example, Pu et al., in a study to explore potential mediators linking race/ethnic

disparities to reduced receipt of preventive care found that patients were less likely to receive diabetes preventive care if they were younger in age, Hispanic, resided in rural areas, had lower family income and were uninsured.<sup>12</sup>

While implementing preventive care measure on a population scale can be costly, the potential long-term health benefits can certainly offset the healthcare expenditures over time. To date, many published studies of preventive care services focused solely on individuals who are diagnosed with diabetes alone.<sup>113,122</sup> However, preliminary data suggests that comorbid depression may have an effect on use of preventive services among other treatment recommendations persons with diabetes.<sup>49,112,123,124</sup>

There is a paucity of conclusive research concerning use of diabetes specific preventive care service in patients suffering from comorbid depression and diabetes with some studies yielding an increased rate of receipt of diabetes preventive care<sup>49,125,126</sup> while others indicating lower degree of use<sup>82,127,128</sup> or no significant association.<sup>129,130</sup> For example, Lin et al. conducted a study of 4,463 patients in a large health maintenance organization to assess whether diabetes self-care, medication adherence, and use of preventive services were associated with depressive illness.<sup>112</sup> This study did not find an association between major depression and receipt of preventive services for diabetes. In contrast, in a study of 4,398 adult health plan members with diabetes conducted by Simon et al, reported that depression was associated with lower visit rates for preventive services.<sup>82</sup> Given the conflicting evidence on the use of preventive services in patients with both diabetes and depression and the need for improvement in the levels of preventive service use,

we sought to quantify the effect of comorbid depression on rates of preventive service utilization.<sup>70,131</sup> For our study, we focused on five important preventive services, including: 1) A1C testing; 2) Diabetic Foot Exam; 3) Lipid check; 4) Influenza Vaccination; 5) Dilated Eye Exam; 6) Routine Medical Checkup.

## 2.2 Methods

### 2.2.1. Study Design and Data source

To achieve the aims of our project, we conducted a retrospective cohort study among adult patients (18 years of age or older) with diabetes. Our study utilized components of the Medical Expenditure Panel Survey (MEPS), a publicly available dataset collected by the Agency for Healthcare Research and Quality (AHRQ).<sup>132,133</sup>

MEPS is a large-scale nationally representative survey of U.S. non-institutionalized population, medical providers, and employers. The MEPS utilizes a national probability-sampling scheme and collects household and individual-level data on medical service utilization information and can be used for cross-sectional or longitudinal analysis.<sup>134-137</sup> The data set is unique in terms of its sample size, composition and provides a set of variables, which are hypothesized to influence the receipt of diabetes preventive care. The MEPS sampling frame is drawn from a subsample of households included in the previous year's National Health Interview Survey (NHIS) conducted by the National Center for Health Statistics (NCHS).<sup>137</sup> The MEPS sample design includes stratification, clustering, multiple stages of selection, and over sampling of certain racial and ethnic minority populations.<sup>136,137</sup>

To achieve the aims of the MEPS, AHRQ employs an overlapping panel designs (Appendix 2.2) approach to identify preliminary contacts followed by interviews during five separate in-person rounds with purposeful oversampling of certain groups (e.g., low income, racial minorities).<sup>138</sup> A new panel of sample households is selected

each year, and data for each panel are collected during two consecutive calendar years. The overlapping design of the MEPS provides information on the same people several times during the year, allowing for repeated observation analyses.<sup>139</sup> To account for the complex design and sampling scheme of the MEPS, sampling weights are published for each survey which when utilized adjusts for the complex survey design and survey nonresponse. In addition, the weights allow extrapolation to reflect rates of medical service utilization in the US general population as derived from the Current Population Survey.<sup>133,136,137,140</sup>

In addition to the overarching design of the survey, the MEPS collects several types of data that are useful for conducting healthcare research. There are three principal components of the survey; the Household Component (HC), the Insurance Component (IC), and the Medical Provider Component (MPC).<sup>141</sup> For this study, we included the HC and several sub-surveys that were useful for our analyses. The household component (HC) file of MEPS, considered the core survey, collects demographic characteristics, health conditions, self-rated health status, medical services use, access to care, satisfaction with care, health insurance coverage status, and income for each person surveyed for a period of two years.<sup>136,139</sup> During interviews, all participants are also questioned regarding healthcare use services and medical and mental health treatment including prescription drugs and mental health counseling. Within the HC, the Medical Conditions (MC) file reports information on health conditions and procedures reported by respondents during the survey. The medical conditions and procedures reported by the household component

respondent are recorded by the interviewer as verbatim text, which is then coded by professional coders to fully specified International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, including medical condition and V codes.<sup>142</sup> However, to preserve confidentiality, the MEPS data includes only 3-digit ICD-9 CM codes in the publicly available research files. To foster data analyses, the MEPS data provide Clinical Classification Codes (CCCs), derived by using the Clinical Classifications Software (CCS) disease categorization scheme which aggregates ICD-9-CM codes into clinically meaningful categories, grouping similar conditions into one CCC. To minimize underreporting of medical conditions and procedures, the interviewers use a variety of techniques.<sup>137</sup>

Since we were primarily interested in assessing the use of preventive care in patients with comorbid depression and diabetes the preventive services for diabetes, we specifically utilized the Diabetes Care Survey (DCS) supplement.<sup>143</sup> The DCS a special self-administered paper-and-pencil questionnaire fielded Rounds 3 and 5. Households received a DCS based on their response to question regarding a health professional communicating with the individual that he or she has diabetes. The DCS specifically collects information regarding the diabetes related medical care that is received by the patients, including medications and previous diagnostic tests including the receipt of preventive services by the individual in the recent past. Linking this survey, administered once a year over two years, with the household components enables a complete examination of the diabetes related health care received by the patient.<sup>136</sup>

### *2.2.2 Study Cohort*

To gain adequate sample size and construct an analytical study cohort for our analyses, we selected data for individuals from households in Panels 12, 13, 14, 15, 16 coinciding to MEPS survey years of 2008-2011. Data for each year was constructed based on six rounds of interviews, rounds 1-3 for the panel that was initiated that year and rounds 3-5 for the panel that was initiated in the previous year. Information attained in each round of the interviews pertains to a specific frame of time known as reference period. Thus, the study reference period begins from 1<sup>st</sup> January 2008 for panel 12 round 5 and ends on 31st December 2011, which is the end of the last reference period. Table 2.1 provides an overview of the panels and rounds from which the study cohort was selected with respect to the year. Within these included years, we focused on all respondents aged 18 years or older, who self-reported a diagnosis of diabetes with a positive sampling weight.

### *2.2.3 Cohort Eligibility-Identification Of Diabetes*

We defined the inclusion criterion for the study sample as the presence of diabetes in individuals, with or without comorbid depression. We identified diabetes-using patient self-report in answering to survey question regarding diabetes, where respondents were asked, "Have you ever been told by a doctor that you have diabetes?"<sup>143</sup> If the individual responded affirmatively, we considered them eligible for entry into the final cohort. Individuals who were aged 17 years or younger and those who responded "not sure," "don't know," "refused" or "missing." were



considered ineligible<sup>59</sup>. Similarly, we excluded cases of gestational diabetes. During the process of this survey, every person who reported to have received a diagnosis of diabetes was further asked to complete the DCS. In previous studies, Richard et al. and Dismuke et al. have utilized similar procedures to recognize diabetic population in this dataset to investigate the racial disparities in the quality of diabetes care and association between major depression, number of depressive symptoms and personal income among the diabetic population respectively.<sup>68,139</sup>

#### *2.2.4 Exposure Definition-Comorbid Depression*

To conduct our retrospective cohort study, we created two groups, 1) those with comorbid depression, and 2) those without comorbid depression. We identified study participants with depression using individual's self-reports as well as diagnosis codes captured on the MC survey. As part of the MC survey, the two-item, Patient Health Questionnaire (PHQ-2) is collected from participants. The PHQ-2 is a previously validated instrument to identify depression. The PHQ-2 was designed to report the feelings of depressed mood and anhedonia in patients over the past 2 weeks, with the scores ranging from 0 ("not at all") to 3 ("nearly every day") for each criterion. Kroenke et al. reported that the PHQ-2 has a 83% sensitivity and 92% specificity for identifying major depression.<sup>144,145</sup> Utilizing this information, we identified survey respondents with a score of  $\geq 3$  on the PHQ-2 as having comorbid depression. To comprehensively identify persons with depression and taking into account some respondents may have not demonstrated signs of depression at the

time of survey (e.g. symptoms managed with antidepressant medication); we further identified individuals who had reported ICD-9 CM codes 311, 296 or a CC code 657 or both. Egede et al. suggested that for approximately 70% of the MEPS population in the year 1996, ICD 9 CM code 311 was appropriate.<sup>49</sup> Kim et al. in a study to assess the impact of workplace injury on depression and identify the potential risk factors associated with post-injury depression in the US working population, used ICD 9 CM codes 296 and 311 to identify depression in the study population.<sup>146</sup> Similarly, Bhattacharya et al. identified depression using the CCC 657 to examine the excess risk of chronic physical conditions associated with depression.<sup>147</sup> Frayne and colleagues developed an algorithm to identify the patients with depression, which utilizes a more inclusive set of codes, namely 296 and 311.<sup>148</sup>

The prevalence of depression in the final study cohort was 25.8% with 1,208 patients suffering from depression as identified by the self-reported PHQ-2, ICD 9 CM/CC codes or both. Of the 4,668 identified respondents, 731 had a score of 3 or higher on the depression scale. Of these, 288 had an ICD 9 CM/ CC code for depression while 443 respondents did not record an ICD 9 CM/ CC code for depression. Out of the 3,937 respondents who did not have a score of 3 or higher on the depression scale, 477 respondents (12.1%) had an ICD 9 CM/ CC code for depression and therefore we classified them as having comorbid depression. Thus, the final sample for inclusion included 1,208 persons with depression and 3,460 persons without depression. Figure 2.1 outlines the process of selecting the patients with diabetes and comorbid depression.

### *2.2.5 Outcome: Use of Preventive Services in the Past Year*

The main outcome variable of this study was the suggested use of diabetes preventive care services according to the ADA guidelines. The self-reported receipt of seven recommended diabetes-specific preventative services was examined within the past year using the DCS, based on the inclusion in the MEPS and consistent with the guidelines of the national organizations.<sup>91</sup> For this study, the seven outcomes of focus were annual receipt of:

1. Hemoglobin A1C (A1C) testing
2. Foot exam
3. Dilated eye exam
4. Influenza vaccination
5. Cholesterol testing
6. Blood pressure screening
7. Physical exam

For information regarding the frequency testing of the hemoglobin A1C, the individuals were asked about the number of times a doctor, nurse or other health professional checked their blood for A1C in the past year. In contrast, questions with reference to the remaining preventive care services were constructed in a manner

which asked the respondent to report the last time they underwent a preventive service in the recent past (alternatives restricted to same year, past year, year before past year, not in the past 2 years and never had the preventive service). Using this information, we created seven binary outcome variables for each of the self-reported preventive health care utilization over the prior year. Table 2.2 summarizes the MEPS questions asking about use of these services, the coding scheme for the receipt or no receipt of these services and the ADA recommendations for the services.<sup>91</sup> During the study, respondents with missing data reported for any of the preventive services were considered ineligible for further analyses.

#### *2.2.6 Identification of Potentially Confounding Factors*

Based on the available literature, we identified and evaluated a set of socio-demographic characteristics that was associated with differences in the use of preventive care services in patients with comorbid depression and diabetes. The variables describing demographic status of the person were constructed as per the self-reported status of the person on the 31st of December of the survey year. These variables are updated in every round of data collection. Since the DCS was a cross-sectional survey, the variables represented current status only. In our study analyses, some categories of the variables were merged and reconstructed to have a preferable distribution of the population within these categories. These factors included age (18–34 years, 35-49 years, 50-64 years and 65 and above), gender (male versus female), marital status (married, widowed/divorced/separated and never

married), race/ethnicity (Hispanic, White non-Hispanic, black non-Hispanic and others), income level based on the federal poverty line (FPL) (poor/near poor [ $<125\%$  FPL], low income [ $125\% - <200\%$  of FPL], middle income [ $200\% - <400\%$  of FPL] and high income [ $>400\%$  of FPL]), educational status (less than a high school degree, high school degree, advanced education and others), perceived health status (excellent or very good, good and others), health insurance status (private insurance coverage, public insurance coverage only, uninsured), insulin use (Yes versus No), Metropolitan Statistical Area (MSA; MSA versus Non-MSA), employment status (Employed versus not employed), Body Mass Index (BMI; underweight [BMI  $<18.5$ ], normal weight [BMI  $\geq 18.5$  and  $\leq 24.9$ ], overweight [BMI  $\geq 25.0$  and  $\leq 29.9$ ] and obesity [BMI  $\geq 30.0$  ]) and smoking status (Yes versus No).

### *2.2.7 Identification of Comorbidities*

Based on the available literature, we identified and evaluated a set of socio-demographic characteristics that was associated with differences in the use of preventive care services in patients with comorbid depression and diabetes. The variables describing demographic status of the person were constructed as per the self-reported status of the person on the 31st of December of the survey year. These variables are updated in every round of data collection. Since the DCS was a cross-sectional survey, the variables represented current status only.<sup>15</sup> In our study analyses, some categories of the variables were merged and reconstructed to have a preferable distribution of the population within these categories.<sup>138</sup>

Comorbidities were defined by using the patients' clinical records in the medical conditions file. The CCCs were used to identify presence of clinically relevant comorbidities. The methodology defined by Machlin et al. was used to select comorbidities based on sample size considerations and relevance to association with use of preventive care services.<sup>149</sup> Single or multiple CCCs were chosen to define each comorbidity and the presence of each comorbidity was recorded as a dichotomous variable. Appendix 2.3 provides more detailed information on the identified comorbidities including the CCCs that utilized to ascertain each of the comorbidities.

#### *2.2.8 Statistical Analysis*

As we conducted a retrospective cohort study, we conducted all analyses comparing the two created exposure groups, those with comorbid depression (n= 1,208) and those without comorbid depression (n= 3,460). We first checked for comparability in background characteristics of the two groups focusing on age, gender, comorbidity conditions, and other aforementioned socio-demographic factors. This was done to understand and profile the study population and identify potentially confounding factors between the two groups. We generated descriptive statistics within each of the groups including means and standard deviations for continuous variables and percentages were reported for categorical variables. We examined differences between the two exposure groups using the Pearson's chi-square test or Fisher exact test for categorical variables and T tests for continuous variables.

After baseline comparison of the two exposure groups, we next assessed the prevalence of use of preventive care service use in the diabetic population with and without depression. Percentages were reported to compare the use of preventive services between diabetic individuals with and without depression. To further quantify the effect of comorbid depression on use of preventive services after controlling for confounding, we employed logistic regression modeling. We identified potentially confounding variables that varied between the two exposure groups (during bivariate analyses). In addition to these, variables of known clinical importance (age, gender race/ethnicity) were selected as potential confounders.

Initially, we constructed unadjusted odds ratios for use of preventive care services in diabetic patients with and without comorbid depression. Then, we used a series of multivariate logistic regression models to determine the independent effect of comorbid depression on the use of preventive services. Controlling for all the aforementioned patient level covariates that might influence the use of preventive services, we calculated the adjusted odds of receiving at least 2 A1C tests, a diabetic foot examination, an eye examination, an influenza vaccination, a blood cholesterol check and a routine medical checkup in the past year. Because of the complex survey design of the MEPS HC file, we used special diabetes weights from MEPS to compute robust standard errors of the estimates.<sup>150</sup>

During the process of building the logistic regression models for each mentioned preventive care services individually, we used a non-computer generated stepwise

approach. Variables that were identified as potential confounders in the bivariate analysis were added to the model for each service sequentially in the order on the largest significant difference between the depressed and non-depressed groups with respect to the particular variable. Thus, nested models were fitted in an iterative, manual process using an inclusion threshold of a 10% change in the  $\beta$  estimate of the principal independent variable, comorbid depression (indicator of exposure group). Iterations continued in this manner until the most parsimonious model was fitted. At the end of this process, we added all the excluded variables back to the final model to assess the potential for residual confounding. This model with all the variables was compared to the final model constructed at the end of the stepwise process. We used the Akaike Information Criterion (AIC) at this step of the model building process since AIC is asymptotically equivalent to cross-validation and the bootstrap, two most popular validation methods. We conducted a Hosmer and Lemeshow Goodness-of-Fit Test to examine the fit of the model as well as a likelihood ratio test to evaluate the final fitted model<sup>151-154</sup>. We further assessed multicollinearity in the model. For this purpose, we used the variation inflation factor (VIF), tolerance and eigenvalues to make the decisions on exclusion of collinear variables. These were calculated utilizing a separate regression model and specifically using the VIF, TOL, and Collin options. If two variables were found collinear, we included the variable that was clinically more relevant to our analysis. All statistical tests were conducted with two-tailed alpha 0.05. At the end of this process, we compared the models using the above procedures and selected the best fitting model. We then reported



multivariable (adjusted) odds ratios (AORs), including their respective 95% confidence intervals (95% CI).

Due to the clustered and correlated nature of the survey data, analyses were conducted using SAS software, Version 9.3 (SAS Institute Inc., Cary, N.C.) and SAS callable SUDAAN, Release 9.0.1 (Research Triangle Institute, Research Triangle Park, N.C.) to account for complex survey design.<sup>155</sup> This study was reviewed and approved as exempt by the University of Rhode Island's Institutional Review Board.

## 2.3 Results

### 2.3.1 Final Cohort

Within the four years of MEPS data utilized for our analyses (2008-2011), we identified 138,030 survey respondents included in the dataset. Figure 4 describes the steps that were followed for the selection of final cohort of respondents. As per the recommended data estimations procedures, we did not consider respondents with non-positive person level weights for further analyses since only data for persons with a positive person-level weight can be used to make estimates for the civilian non-institutionalized U.S. population. Further, we restricted the population to respondents who were above 17 years of age, who had responded “yes” to the question regarding diabetes and had a positive diabetes weight, which adjusts for DCS nonresponse and weights to the number of diabetics in the US civilian non-institutionalized population. This selection process resulted in the initial sample of 7,780 respondents with diabetes. Out of this population, only the respondents who had information on all the required variables were selected for the study. Thus, the final sample for the study comprised of 4,468 respondents. This sample size represented 60% of the population that was eligible for the study.

The prevalence of depression in the final study cohort was 25.78% with 1,208 patients suffering from depression according to the self-reports of PHQ-2 or ICD 9 CM/CC codes or both (Figure 2.1). Moreover, 288 patients had depression according to the PHQ score as well as ICD 9 CM/ CC code for depression while 443 respondents

did not record an ICD 9 CM/ CC code for depression even though they had a PHQ score 3 or more. Out of the 3,937 respondents who did not have a score of 3 or higher on the depression scale, 477 respondents had an ICD 9 CM/ CC code for depression and were considered as suffering from comorbid depression.

### *2.3.3 Demographic and Clinical Characteristics of the Cohorts of Individuals With and Without Depression*

Table 2.3 presents an overview of the descriptive statistics of the final sample of individuals with diabetes and compares the demographics characteristics of the sample by depression status. With respect to depression status, those with existing comorbid depression were primarily between ages 50 and 64 (42.2%), females (59.2%), married (50.88%), high school graduates (49.1%) and non-Hispanic whites (72.7%). A high fraction of these respondents with depression had a fair or poor perceived health status (55.04%), private health insurance coverage (54.1%), did not use insulin (63.2%), resided in metro areas (78.6%), were not employed (65.2%), were overweight (87.1%), were nonsmokers (79.2%) and had a primary care physician (94.6%).

Apart from a few variables (metro status, primary care provider status and insulin use), all the other variables demonstrated statistically significant differences with respect to the depression status among individuals with diabetes. With respect to the age groups, people with diabetes and comorbid depression were more likely to be in the age groups 35-49 (17.8%) and 50-64 (42.2%) as compared to people without

comorbid depression (15.4% and 36.9% respectively  $p=0.002$ ). In contrast, people without comorbid depression were more likely to be in the age group 65 and above (38.7% vs 30.7%). With respect to gender, the proportion of women in the comorbid depression group was higher as compared to those in the non-depressed group (59.2% vs 48.5%,  $p < 0.001$ ). Individuals with diabetes and depression were more likely to be unmarried as compared to people suffering from diabetes alone (49.1% vs 36.8%,  $p < 0.001$ ). In contrast, the percentage of people without comorbid depression and diabetes was significantly higher in the high income group as compared to the people with comorbid depression and diabetes (40.6% vs 25.9%,  $p < 0.001$ ). The prevalence of higher education was significantly lower in the respondents with comorbid depression and diabetes as compared to the respondents without comorbid depression (16.4% vs 23.3%,  $p = 0.001$ ). With respect to the racial and ethnic distribution of the population, people with comorbid depression and diabetes are more likely to be non-Hispanic whites as compared to the diabetetic people without depression (72.7% vs 66.8%,  $p=0.003$ ). A significantly higher proportion of people with comorbid depression and diabetes reported being in fair or poor health status in contrast to the individuals with only diabetes (55.0% vs 25.0%,  $p < 0.001$ ). In comparison to the individuals without depression, people with depression were more likely to have some form of public insurance (37.7% vs 25.7%,  $p < 0.001$ ). There was a lower proportion of depressed people with current employment (34.5% vs 50.2%,  $p=0.001$ ) and normal BMI status (10.2% vs 14.2%,  $p = 0.013$ ) in contrast to the non-depressed diabetetic individuals. Respondents with

comorbid depression and diabetes were more likely to be smokers than the respondents with diabetes alone (18.6% vs 12.8%,  $p < 0.001$ ).

The prevalence of selected comorbidities was significantly higher in diabetes patients with comorbid depression as compared to the patients with diabetes alone. Table 2.4 outlines the differences in the diabetic patients with and without comorbid with respect to the presence of clinically significant comorbidities. It could be seen that heart disease (16.4% vs 10.4%,  $p < 0.001$ ) and injury (16.1% vs 11.2%,  $p = 0.005$ ) were reported more frequently in diabetes patients with comorbid depression relative to patients suffering from diabetes alone. Similarly, back disorders (23.6% vs 15.2%,  $p < 0.001$ ), upper respiratory disorders (20.1% vs 14.1%,  $p = 0.003$ ) and thyroid disorders (17.3% vs 13.2%,  $p = 0.023$ ) had a higher prevalence in patients with comorbid depression and diabetes. Overall the most prevalent comorbidity for patients in the final cohort was hypertension, with patients suffering from comorbid depression and diabetes having a higher occurrence of hypertension than the patients with diabetes alone (78.6% vs 73.0%,  $p = 0.004$ ). Similarly, the reported rates for hyperlipidemia were high and differences between the diabetic patients with and without depression were remarkable (74.2% vs 67.9%,  $p = 0.001$ ). The occurrence of cerebrovascular disease (8.4% vs 4.9%,  $p = 0.004$ ), urinary tract infections (9.3% vs 6.4%,  $p = 0.037$ ), headaches (11.6% vs 4.3%,  $p < 0.001$ ) and anemia (6.6% vs 4.2%,  $p = 0.018$ ) was also higher amongst the diabetic patients with comorbid depression. Differences in the rates of kidney disease (6.8% vs 6.6%,  $p = 0.874$ ) and eye disorders (10.1% vs 9.3%,  $p = 0.554$ ) were not significantly different in the diabetic patients with

and without comorbid depression. Similarly, the prevalence of epilepsy and convulsions (1.9% vs 0.9%,  $p=0.077$ ), gall bladder disease (2.4% vs 2.1%,  $p=0.713$ ), hernias (3.1% vs 2.3%,  $p=0.322$ ) and osteoporosis (3.0% vs 2.8%,  $p=0.758$ ) was relatively low and not significantly different between the two groups. In summary, the most frequently occurring comorbidities in the final cohort hypertension, hyperlipidemia, and back disorders while the least prevalent comorbidities were epilepsy and convulsions, gall bladder disease and osteoporosis.

#### *2.3.4 Prevalence of Use of Preventive Care Services In the Diabetic Population*

Table 2.5 describes the estimates of diabetes specific preventive care behaviors. In the final sample, about 79.1% of the people reported having undergone an A1C test in the previous year. Similarly, about 52.1% of the respondents reported having undergone an annual diabetic foot examination in the past 12 months while 65.8% of the sample reported having their blood cholesterol in the previous year. About 49.9% of the individuals with diabetes reported taking an influenza vaccine in the past year while 51.2% reported having a retinal eye examination performed during the past one year. Majority of the respondents indicated that they underwent a blood pressure check (96.8%) and a routine medical checkup (89.1%).

Examining the trends in the use of these services, it could be seen that there were significant changes observed over the four years of data for some preventive care services. There was a steady increase in the rate of A1C testing, with 83.5% of the respondents reporting undergoing an A1C test in past year for data year 2011 as

compared to the 79.1% who disclosed testing for A1C in the last year for data year 2008. Similar results could be seen for the diabetic foot exam, in which case the rate for testing in the past year rose from 49.8% in 2008 to 56.4% in 2011 representing a weighted increase of almost 7 percentage points. Rates for blood cholesterol checks progressed from data year 2008 (65.0%) to data year 2010 (73.4%) but exhibited a slight decline for the data year 2011 (72.9%). The number of respondents who reported taking an influenza vaccination also displayed an increase of approximately 6% from data year 2008 (50.0%) to data year 2011 (56.3%). There was a significant rise in the number of people who reported having a retinal eye examination in the previous year with 49.2% respondents having undergone the test in data year 2008 and 58.6% respondents having their eyes tested in data year 2011.

Figure 2.3 describes the differences in the use of preventive services by presence or absence of comorbid depression. It was seen that people with comorbid depression (82.4%) had a higher rate of undergoing more than one A1C test in the previous year as compared to people without comorbid depression (80.4%). Similar results were found for annual diabetic foot exams (56.6% vs 52.3%), annual lipid check (71.1% vs 68.8%), annual influenza vaccination (53.7% vs 52.7%) and blood pressure checks (98.1% vs 97.3%). In contrast, with respect to annual dilated eye examinations (52.3% vs 54.0%) and annual routine medical checkup (88.6% vs 90.6%), people without comorbid depression had a higher rate of receipt of these services.

*2.3.5 Multivariable Modeling-the Effect Of Comorbid Depression On The Receipt Of Diabetes Preventive Care Services.*

Crude and adjusted odds ratios with the 95% confidence intervals from multivariate logistic regression models describing the associations between presence of comorbid depression in diabetes and receipt of the preventive care services are described in Table 2.6. Among patients with diabetes, patients with depression were significantly more likely to receive >1 A1C tests in the previous year (Crude Odds Ratio [COR] 1.19; 95% Confidence Interval [CI] = 1.01-1.44). However, after adjusting for confounding factors the receipt of A1C tests were not statistically significant (Adjusted Odds Ratio [AOR] = 1.03; 95% [CI] 0.83-1.28). Similarly, in unadjusted analyses, patients suffering from comorbid depression and diabetes are 20% more likely to receive an annual diabetic foot exam as compared to patients without comorbid depression (COR =1.20; 95% [CI] 1.01-1.44), which did not persist after adjustment (AOR= 1.12; 95% [CI] 0.94-1.34). The unadjusted odds of patients with comorbid depression and diabetes receiving an annual lipid check were slightly higher than diabetic patients without depression (COR =1.11; 95% [CI] 0.94-1.32). These differences, however, were statistically insignificant. In adjusted analyses, depression had an insignificant association with the receipt of an annual lipid check in patients suffering from comorbid diabetes and depression (AOR= 1.07; 95% [CI] 0.88-1.30; p=0.47). The association between receipt of an annual influenza vaccination and presence of comorbid depression in diabetes was statistically insignificant in both unadjusted (COR =1.06; 95% [CI] 0.88-1.28; p=0.66) as well as adjusted analysis (AOR= 1.02; 95%



[CI] 0.83-1.25;  $p=0.87$ ). Depression was not significantly associated to the receipt of an annual dilated eye examination in patients with diabetes. The odds of receiving an annual dilated eye exam was marginally lower for patients with comorbid depression and diabetes in both unadjusted (COR =0.94; 95% [CI] 0.79-1.11;  $p=0.45$ ) and adjusted analyses (AOR= 0.93; 95% [CI] 0.76-1.12;  $p=0.44$ ), but these differences were statistically insignificant after adjusting for confounding factors.

Contrary to other preventive services, before adjusting for the specified confounders, people with comorbid depression and diabetes were less likely to receive a routine medical checkup as compared to the diabetic patients without depression (COR =0.80; 95% [CI] 0.63-0.99;  $p=0.04$ ). However, similar to the results for other preventive services that were explored, these differences between people with and without depression were not significant after controlling for various socio-demographic and clinical factors.

## *2.4 Discussion*

Using a nationally representative probability survey, we performed a study that had 2 principal goals. The first was to examine patterns of preventive care service use among individuals with and without diabetes using data on non-institutionalized civilian US population. The second was to examine the relationship between the status of comorbid depression and receipt of diabetes specific preventive health practices. This study advances the current body of literature regarding the differences in the quality of preventive care in diabetic patients with and without comorbid depression by exploring the impact of depression as an independent factor on receipt of these services.

The ADA recommends that diabetic patients have their blood A1C test done twice a year if their glycemic control is meeting its goals and quarterly in case of poor glycemic control or changes in diabetic management. The ADA further recommends diabetic patients to undergo certain other preventive care practices like diabetic foot exam, retinal eye exam, influenza vaccination, blood cholesterol check and a routine medical checkup annually.<sup>91,156</sup> From the results of this study, we conclude that a significantly high percentage of the American diabetic population that was studied did not receive the recommended standard of care, thus highlighting the need and opportunity for improvement in the status of preventive care among adults with diabetes. For instance, nearly half of the study population did not receive a diabetic foot exam, influenza vaccination and dilated eye exam in the past year. In this study,

we observed that the levels of use of certain preventive services were considerably lower than those previously reported.<sup>22,116</sup> For example, Harris et al. in a study of the Behavioral Risk Factor Surveillance System data examining the change in rates of adults with diabetes receiving 4 essential preventive care services found that the overall age adjusted rate of receiving all 4 preventive care services increased from 10% in 1997 to 20% in 2007, but remained suboptimal. In the same study the proportion of adults receiving an annual foot examination was reported as 69% while that of receiving a pneumococcal vaccination was much lower at 39%.<sup>157</sup> Beckles et al assessed the use of preventive care services, concluding that most adults do not meet recommendations for standards of diabetes care with only 72% of the patients visiting a health care provider for diabetes care at least once, 61% having their feet inspected at least once, and 61% reporting having received a dilated eye exam.<sup>118</sup> Moreover, Pu at al reported that among diabetes patients, 74% received the recommended levels of A1C tests, compared to 65% getting a foot exam and an 63% receiving an eye exam.<sup>12</sup> Moreover, based on a cross-sectional observational study conducted by Wang et al. using the Medical Expenditure Panel Survey (MEPS) from 2005, the percentage of people receiving an annual diabetic foot exam, annual cholesterol check and annual influenza vaccination was demonstrated to be 74.3%, 89.5%, 57.5%, respectively.<sup>22</sup> Similarly, according to a study based on National Health and Nutrition Examination Survey (NHANES) and Behavioral Risk Factor Surveillance System survey (BRFSS), the proportions of annual foot exams (68.3%), annual cholesterol checks (84.6%), and annual influenza vaccinations (52.5%) were all

suboptimal. According to the Centers for Disease Control and Prevention (CDC), the age adjusted estimates of adults >18 years of age who reported receiving preventive care practices were 68.5% for receiving > 1 A1C test and 67.5%, 50.1% and 62.8% for an annual diabetic foot exam, influenza vaccination and dilated eye exam respectively.<sup>158</sup> Gold et al. in a study of patients receiving care at Federally Qualified Health Centers (FQHCs) found that 32% of OCHIN (Our Community Health Information Network) patients with diabetes received a flu vaccination in 2005, 36% an LDL screening, 54% at least one HbA1c screening, and 21% a nephropathy screening. In our study, the proportions observed on these services were 81.0%, 53.4%, 69.4%, and 53.5% respectively for >1 A1C tests, annual foot exam, annual cholesterol check, annual influenza vaccination and annual dilated eye examination in the previous year. This suboptimal use of preventive services is a major concern for policy makers since the benefits of implementing these services on reducing the mortality as well as micro- and macro-vascular complications of diabetes are well documented. It has also been reported widely in literature that timely receipt of foot care and eye examinations reduce the risk of foot complications by 50-60% and that of severe vision loss by approximately 60% in people with macular edema and 90% in people with proliferative retinopathy.<sup>156</sup> Thus, it is imperative that strategies be designed to ensure effective mechanisms are in place to deliver preventive care that adheres to the standards recommended by the ADA.<sup>156</sup>

Our study demonstrates that depression is not significantly associated with increased use of the recommended diabetes preventive care services. To our best knowledge,

this study adds substantially to the scarce literature that examines the effect of depression on the use of diabetes specific preventive care services. Other studies have yielded inconclusive findings with respect to differences in the utilization of preventive services in patients with and without depression.<sup>112,127,128,130,159</sup> Before adjusting for clinically relevant covariates, presence of depression was associated with associated with the receipt of three diabetes specific quality of care indicators within the past year—an A1C measurement, a diabetic foot check, a retinal eye examination, with depressed people more likely to undergo the recommended levels of A1C testing and diabetic foot testing but less likely to undergo a retinal eye examination. However, after controlling for various demographic and health characteristics, we found that comorbid depression did not significantly influence the likelihood of receipt of these services. Our findings are consistent with some previous conducted studies that have concluded that presence of depression is not associated with higher use of preventive care services.<sup>124,128,156,160</sup> Lin et al. found that major depression was mainly associated with patient-initiated behaviors that are difficult to maintain (e.g., exercise, diet, medication adherence) but not with preventive services for diabetes.<sup>112</sup> Similarly, Egede et al. in a study to examine the effect of minor and major depression on self-care behaviors and quality of care among adults with diabetes, found no significant association between both major as well as minor depression and use of preventive care services like A1c testing (AORs 1.02, 95% CI[0.80 – 1.31] and 0.84, 95% CI [0.68 – 1.04] respectively) and diabetic foot exams (AORs 0.88, 95% CI [0.72 – 1.08] and 0.81, 95% CI [0.62 – 1.04] respectively).<sup>128</sup> Desai

et al. studied the relationship between mental disorders and quality of diabetes care in a national sample of veterans and found that diabetic patients with or without depression did not differ significantly with respect to the receipt of A1C tests (AOR 0.98, 95% CI [0.88 – 1.08]) and diabetic foot examinations (AOR 1.06, 95% CI [1.00 – 1.12]).<sup>130</sup> Similarly, Hutter et al. in a meta-analysis to review the impact of comorbid mental disorders on healthcare costs in persons with diabetes reported inconclusive evidence for differences in the use of retinal eye examinations.<sup>159</sup>

The results of our study are in contrast to some studies in the literature that conclude that coexisting major depression was associated with lower rates of preventive care service use in patients with diabetes and comorbid depression than in those without depression.<sup>112,128,159</sup> For example, Jones et al. compared the use of preventive health services among diabetes patients with and without mental disorders during the years 1996 – 2001 and demonstrated a lower hazard ratio (HR) of A1C determinations (HR 0.92; 99.9% confidence interval [CI] 0.87-0.97) as well as cholesterol checks (HR 0.92; 99.9% CI 0.86-0.98) in patients with diabetes and mental disorders.<sup>127</sup> Moreover Egede et al., after adjusting for clinically relevant covariates, individuals with minor and major depression were significantly less likely to receive a dilated eye examination (AORs 0.81, 95% CI [0.66 – 0.99] and 0.70, 95% CI [0.54 – 0.89] respectively) in the past year and a flu shot in the past 12 months with the latter significant only in patients with minor depression (AOR 0.79, 95% CI [0.65 – 0.95]).<sup>128</sup> Similarly, Simon et al. assessed the contribution of depression as one of the factors affecting health service costs in adults with diabetes and found that rate of

outpatient preventive care visits in patients with diabetes and depression was lower as compared to those without depression (SMD  $-0.09$  [95% CI  $-0.16, -0.01$ ]).<sup>82</sup>

The likely explanation for the non-significant results with respect to depression and receipt of preventive services is that various patient characteristics likely affect the rates of service receipt. In our study, depression was not found to be a significant factor increasing the frequency of A1C testing. However, factors like age, race and ethnicity, income levels, BMI status, marital status, insulin use, presence of a primary care provider and comorbidities like hypertension, hyperlipidemia, and anemia were found to be significant predictors of A1C testing. These findings are similar to other studies analyzing the effects of patient characteristics on receipt of diabetes services.<sup>12,113</sup> DeVeo et al. conducted a secondary analyses of data from 6,562 diabetic individuals aged  $>17$  years of age and found that the odds of receiving this test increased with increase in age and in people with higher incomes.<sup>138</sup> Hu et al. found that both non-Hispanic black and other minority adults had a lower likelihood of reporting receiving a hemoglobin A1C measurement at least once in the past year compared with non-Hispanic white adults.<sup>15</sup> He et al. concluded that primary care physicians and practice features seem to steer diabetes preventive services.<sup>24</sup> In contrast, other studies do not find any significant association between these factors and annual testing for A1C.<sup>123</sup> In our study, there no significant association was evident between depression and receipt of a diabetic foot exam after adjusting for various covariates. We observed several other vital patterns in the receipt of this test. Age, race and ethnicity, insulin use and comorbid hyperlipidemia were found to

be significant predictors of the likelihood of undergoing this test. Previous studies have shown some of these factors to be associated with odds of receipt of a diabetic foot exam annually.<sup>12,15,122,138</sup> On the other hand, our results were in contrast to some studies that did not find a significant association between these sociodemographic characteristics and use of preventive services.<sup>118,139,161</sup> In both unadjusted and adjusted analyses, depression was not significantly associated with receiving an annual lipid exam. In adjusted analyses, we uncovered associations between this preventive care service and some independent variables like age, race and ethnicity, insulin use as well as co-existence of hyperlipidemia. Various studies have found age to be significantly associated with the receipt of an annual cholesterol screening.<sup>12,15,138,162,163</sup> With respect to the relationship between race/ethnicity and the likelihood of undergoing an annual lipid exam, our results are corroborated by some studies<sup>12,163</sup> but are in contrast to results of others.<sup>15,138</sup> Although the effect of depression was insignificant on the likelihood of receiving an annual influenza vaccination, we found that in adjusted analyses age, race/ethnicity, insulin use, and comorbidities were significant predictors of a flu shot. Our findings suggesting that other factors (apart from depression) may be related to the lack of receipt of preventive services rather than depression itself. These findings are consistent with previous reports that provide an evidence of a strong association between these factors and receipt of the preventive service.<sup>119,138,163</sup> After we controlled for the effects of all other sociodemographic covariates, depression was not found to significantly affect the receipt of an annual retinal eye examination.



However, as mentioned in the previous literature, we found that several covariates like age, educational status, smoking status, marital status, presence of primary care provider and comorbidities that we adjusted for in the multivariable logistic regressions, had a significant association with the receipt of a dilated eye examination. Richard et al. reported that elderly patients with college degrees were more likely to report receiving an eye examination compared to those who did not complete high school. Similarly, other studies have also concluded that age, marital status, comorbidities.<sup>15,118,138,161,162</sup> Though depression was found to be insignificantly associated with a receipt of a routine medical checkup in the previous year, we found several demographic characteristics that affected the receipt of this recommend quality of care indicator, a finding supported by DeVeo et al. who found a significant association between routine medical check and factors like age, geographic region and income.<sup>138</sup>

The findings of this study are unique and add to the body of literature regarding the impact of depression on diabetes specific preventive care services. It confirms that in a large population of non-institutionalized patients with diabetes, the overall rates of receiving diabetes specific preventive care services are sub-optimal. Though the self-management of diabetes has been widely considered as having a beneficial effect on control of the disease, we found that major gaps in the use of ADA recommended preventive care practices persisted.<sup>118</sup> Our findings suggest that, as reported earlier, there is a need for policy makers and physicians alike to place greater emphasis on diabetes preventive care practices.<sup>59</sup> Many patient related factors contributing to

differing levels of health care use and overall health of patients were found significant in our analyses. Our findings could be vital in the management of diabetic patients with depression since it will allow researchers to focus on specific action areas that need greater importance and attention since they could affect these self-care activities critical to health outcomes.<sup>59</sup> It also highlights an insignificant association between presence of comorbid depression and adherence to ADA recommended levels of diabetes preventive care. Patients that suffered from depression in our study, though statistically insignificant, were marginally more likely to receive these recommended tests. This might be attributed to the higher frequency of visits to the physicians, since most of these are physician-initiated activities.<sup>164,165</sup> Age, racial differences, insulin use, socioeconomic factors and access to care measured by presence of primary care physician emerged as principal factors related to use of diabetes specific preventive care services.

## *2.5 Limitations And Conclusions*

The interesting findings of this study should be viewed in context of some study limitations. Primarily, one limitation was the use of self-report in diagnosing both diabetes and depression and for identifying use of studied preventive services. As with all the observational studies that utilize self-reports in their design, the study had potential for recall bias. Further, MEPS does not provide information about several measures of diabetes severity. For example, the MEPS does not collect information on the presence of micro albuminuria, serum cholesterol levels (LDL-C), or A1C levels in patients. It would be interesting to see if better quality of care results in better health outcomes as measured by these quality indicators.<sup>123</sup> Undiagnosed diabetes as well as severe diabetes is known to be critical factors that affect diabetes care and outcomes. It was not possible to account for these factors.<sup>161</sup> The issue of surveillance bias and measuring the disease severity were beyond the scope of the study. In case of this bias, stratification is often seen as a remedial measure.

In conclusion, our study provides valuable insights into the differences in use of diabetes preventive services with evaluation of the effect of depression as a comorbid condition. The extent of use of preventative services was comparable for diabetic patients with and without comorbid depression but suboptimal overall. Many of the factors that were found significantly associated with the use of preventive services are modifiable and hence strategies and interventions focusing

on these could improve the outcomes in diabetes patients. This data also demonstrates the need to study effective management of depression in diabetic patients since depression potentially affects various self-care activities. Future research should focus on the underlying causes of this suboptimal use of preventive services as well as establishing a causal relationship between depression and self-care behaviors.

**Table 2.1: Distribution of Panels, Rounds, and Population for the Data Years**

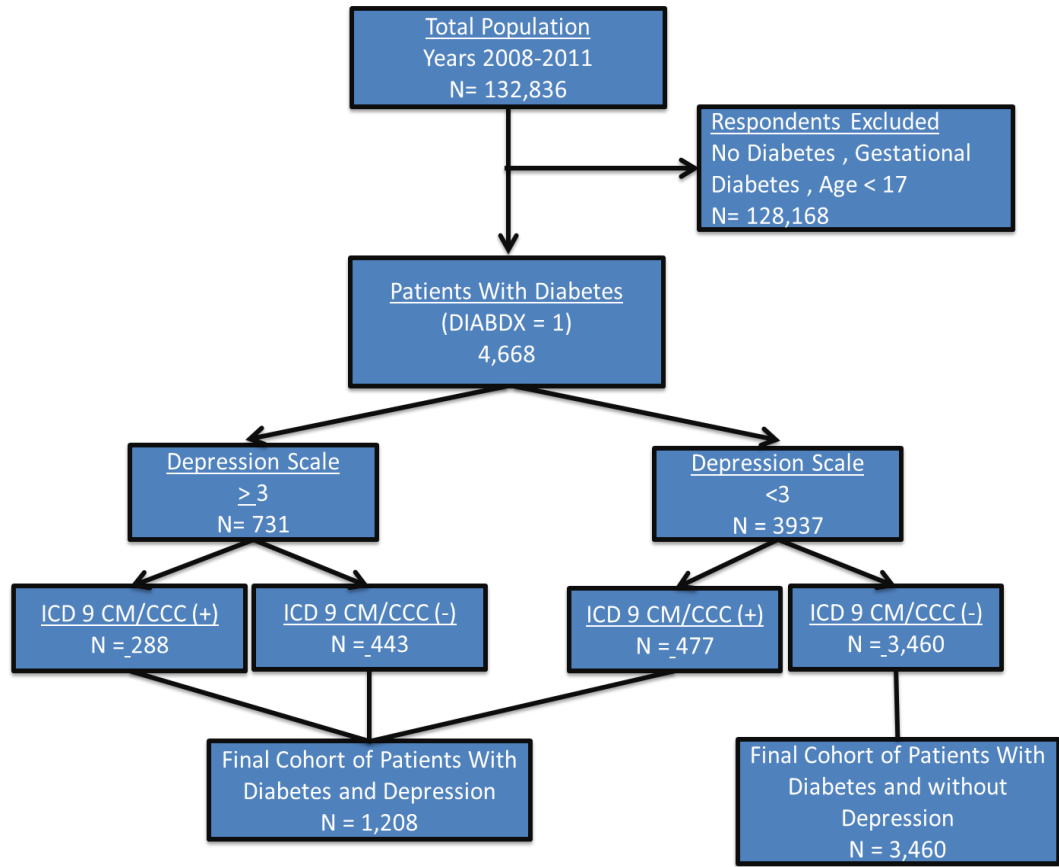
Year	Panels	Rounds	Total Population
2008	12	3,4,5	33,066
	13	1,2,3	
2009	13	3,4,5	34,920
	14	1,2,3	
2010	14	3,4,5	31,228
	15	1,2,3	
2011	15	3,4,5	33,622
	16	1,2,3	

**Table 2.2: Preventive Services: ADA Recommendations, Survey Questions and Coding Schemes<sup>a</sup>**

Preventive Service	ADA Recommendations	Coding Scheme	Survey Questions
A1C Testing	Perform the A1C test at least two times a year.	(0,1)	During 2007, how many times did a doctor, nurse, or other health professional check your blood for glycosylated hemoglobin or "hemoglobin A-one-C"?
Dilated Eye Exam	Perform an annual dilated eye exam.	(0,1)	Which of the following year(s) did you have an eye exam in which your pupils were dilated? This would have made you temporarily sensitive to bright light.
Diabetic Foot Exam	Perform an annual comprehensive foot examination.	(0,1)	Which of the following year(s) did a doctor or other health professional check your feet for any sores or irritations?
Lipid Screening	Perform an annual lipid screening examination.	(0,1)	Which of the following year(s) did you have your blood cholesterol checked?
Influenza Vaccination	Have an annual influenza vaccination.	(0,1)	Which of the following year(s) did you get a flu vaccination (shot or nasal spray)?
Blood Pressure Check	Blood pressure should be measured at each routine visit.	(0,1)	How long since last blood pressure check?
Regular Medical Checkup	Perform an annual medical checkup.	(0,1)	How long since last routine check-up by doctor or other health professional for assessing overall health?

a: Adapted from Standards of medical care in diabetes<sup>91</sup> & Diabetes Care Survey (DCS)<sup>143</sup>

**Figure 2.1: Final Patient Selection To Stratify Patients With And Without Depression**



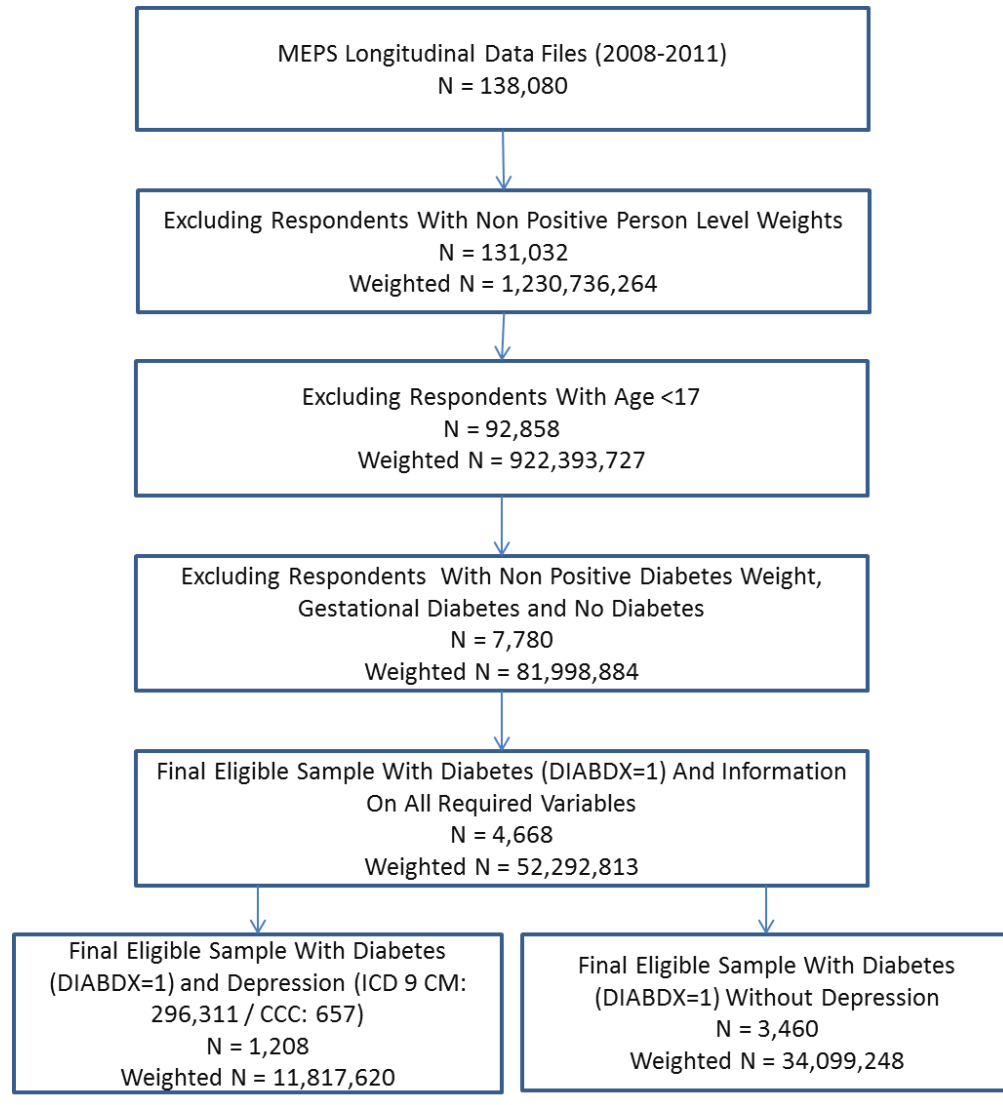
a: DCS Question: Have you ever been told by a doctor or other health professional that you have diabetes or sugar diabetes?

b: Depression Scale: PHQ 2 (Patient Health Questionnaire 2).

c: International Classification of Diseases, Ninth Revision, And Clinical Modification (ICD 9 CM Codes): 296, 311.

d: Clinical Classification Code (CCC): 657.

**Figure 2.2: Selection Of Final Study Population (Weighted)**





**Table 2.3: Demographic Characteristics of U.S. adults with Diabetes  
(Aged >17, MEPS 2008-2011) Stratified By Depression Status**

Variables <sup>a</sup>	DEPRESSION (+)		DEPRESSION (-)		P Value
	Unwtd Freq (1,208)	Wtd %	Unwtd Freq (3,460)	Wtd %	
<b>Age</b>					0.002*
17-34	41	2.9	163	3.9	
35-49	204	17.8	612	15.4	
50-64	513	42.2	1,264	36.9	
65 And Above	377	30.7	1,254	38.7	
Missing	73	6.2	167	4.9	
<b>Gender</b>					<0.001*
Male	440	40.7	1,625	51.4	
Female	768	59.2	1,835	48.5	
<b>Marital Status</b>					<0.001*
Married	591	50.8	2,028	63.1	
Widowed/Divorced/Separated	475	37.6	1,060	27.9	
Never Married	142	11.4	372	8.9	
<b>Income Level</b>					<0.001*
Poor/Near Poor	430	27.4	740	15.1	
Low Income	215	17.1	567	13.7	
Middle Income	330	29.6	1,083	30.5	
High Income	233	25.9	1,070	40.6	
<b>Education Level</b>					0.001*
Less Than High School	408	24.5	973	19.6	
High School	537	49.1	1,531	47.9	
Advanced Education	155	16.4	676	23.3	
Others	100	9.3	270	8.8	
Missing	8	0.5	10	0.2	
<b>Race/Ethnicity</b>					0.003*
Hispanic	276	12.	766	12.3	
White Non-Hispanic	658	72.7	1,563	66.8	
Black Non-Hispanic	208	9.8	818	13.9	
Others	66	4.8	313	6.7	
<b>Perceived Health Status</b>					<0.001*
Excellent/Very Good	147	13.3	986	30.4	
Good	361	31.5	1,478	44.5	
Fair/Poor	700	55.1	996	25.1	
<b>Insurance Coverage</b>					<0.001*
Any Private	552	54.0	2,072	67.1	

Public Only	537	37.7	1,025	25.7	
Uninsured	119	8.2	363	7.1	
<b>Insulin Use</b>					<0.001*
Yes	434	36.6	929	27.1	
No	770	63.2	2,518	72.6	
Missing	4	0.1	13	0.3	
<b>MSA Status</b>					0.029*
Non MSA	246	21.3	587	17.6	
MSA	962	78.6	2,873	82.3	
<b>Employment Status</b>					<0.001*
Employed	367	34.5	1,698	50.2	
Not Employed	840	65.2	1,759	49.5	
Missing	1	0.1	3	0.1	
<b>BMI Status</b>					0.013*
Under /Normal	134	10.2	512	14.2	
Over	1,042	87.1	2,881	83.9	
Missing	32	2.5	67	1.7	
<b>Smoking Status</b>					<0.001*
Yes	222	18.6	425	12.1	
No	953	79.2	2,977	86.5	
Missing	33	2.1	58	1.3	
<b>Primary Care Provider</b>					0.287
Yes	1,131	94.6	3,168	93.2	
No	71	4.9	271	6.2	
Missing	6	0.4	21	0.4	
(+) : Presence of Depression according to the PHQ-242 and/or ICD and CC Codes. (-) : Absence of Depression according to the PHQ-242 and/or ICD and CC Codes. a: n(%) & the Cochran-Mantel-Haenszel statistic / Fischer's Exact Test were used to compare categorical variables. *: Significance at p value 0.05 as derived from ChiSquare					

**Table 2.4: Comorbidities of U.S. adults with Diabetes  
(Aged >17, MEPS 2008-2011) Stratified By Depression Status**

Comorbidity	Unwtd Frequency	Wtd %	Unwtd Frequency	Wtd %	P value
Diabetes W/O Compl. <sup>a</sup>	1,181	98.1	3,334	97.1	0.122
Hypertension	956	78.6	2,497	73.1	0.004*
Hyperlipidemia	889	74.2	2,286	67.9	0.001*
Back Disorders	255	23.6	468	15.2	<0.001*
Lower Resp. Disorders <sup>b</sup>	271	23.5	397	13.5	<0.001*
Upper Resp. Disorders <sup>c</sup>	227	20.1	473	14.1	0.003*
Thyroid Disorders	193	17.3	423	13.2	0.023*
Heart Disease	203	16.4	322	10.4	<0.001*
Injury	186	16.1	356	11.2	0.004*
Headache	125	11.6	159	4.3	<0.001*
Eye Disorders	106	10.1	285	9.3	0.554
Urinary Tract Infections	105	9.3	194	6.4	0.037*
Cerebrovascular Disease	110	8.4	172	4.9	0.004*
Kidney Disease	82	6.8	203	6.6	0.874
Anemia/Deficiencies	84	6.6	147	4.2	0.018*
Diabetes W. Compl. <sup>d</sup>	47	4.2	81	2.6	0.117*
Hernias	38	3.1	61	2.3	0.032*
Osteoporosis	35	3.1	97	2.8	0.758
Gall Bladder Disease	25	2.4	57	2.1	0.713
Epilepsy/Convulsions	19	1.9	41	0.9	0.077*
Cancer	7	0.3	4	0.1	0.327
Substance Abuse	2	0.1	14	0.4	0.051 <sup>^</sup>

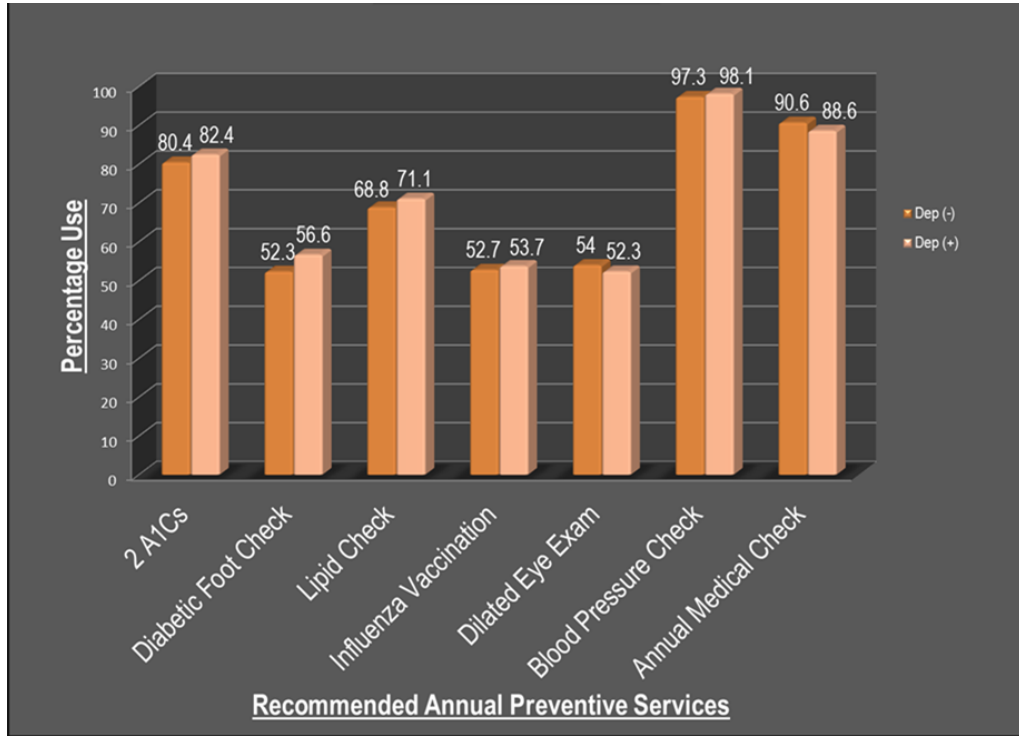
a: Diabetes without complications.  
 b: Diabetes with complications.  
 c: Lower respiratory disorders.  
 d: Upper respiratory disorders.  
 \*: The Cochran-Mantel-Haenszel statistic was used to compare categorical variables. Significance at p value 0.05 as derived from ChiSquare.  
<sup>^</sup>: The Fischer's Exact Test was used to compare categorical variables. Significance at p value 0.05 as derived from Fischer's Exact Test.

**Table 2.5 Frequency Of Preventive Care Service Use Stratified By Year**  
**(2008 – 2011)**

Preventive Service	Year	Total	2008	2009	2010	2011
	Receipt	Unwtd Freq (WTD%)	Unwtd Freq (WTD%)	Unwtd Freq (WTD%)	Unwtd Freq (WTD%)	Unwtd Freq (WTD%)
A1C Tests	YES	3,689 (81.1)	867 (78.9)	946 (79.2)	891 (82.8)	985 (83.4)
	NO	979 (18.9)	254 (21.1)	279 (20.7)	215 (17.2)	231 (16.5)
Diabetic Foot Check	YES	2,433 (53.4)	533 (49.8)	619 (51.6)	599 (54.8)	682 (56.4)
	NO	2,235 (46.5)	588 (50.1)	606 (48.3)	507 (45.1)	534 (43.5)
Lipid Check	YES	3,073 (69.4)	695 (64.9)	775 (66.6)	757 (73.4)	846 (72.8)
	NO	1,595 (30.5)	426 (35.0)	450 (33.3)	349 (26.5)	370 (27.1)
Influenza Vaccination	YES	2,330 (53.1)	530 (50.1)	588 (51.5)	566 (54.4)	646 (56.2)
	NO	2,338 (46.9)	591 (49.9)	637 (48.4)	540 (45.5)	570 (43.7)
Dilated Eye Exam	YES	2,388 (53.5)	527 (49.2)	620 (51.4)	574 (55.1)	667 (58.6)
	NO	2,280 (46.4)	594 (50.7)	605 (48.5)	532 (44.9)	549 (41.3)
Blood Pressure Check	YES	4,517 (97.5)	1,086 (97.4)	1,184 (97.1)	1,074 (98.2)	1,173(97.6)
	NO	151 (2.4)	35 (2.5)	41 (2.8)	32 (1.7)	43 (2.3)
Routine Medical Check	YES	4,158 (90.1)	977 (87.9)	1,076 (88.6)	986 (90.6)	1,119 (93.1)
	NO	510 (9.8)	144 (12.1)	149 (11.3)	120 (9.4)	97 (6.9)

**Figure 2.3: Comparing The Utilization Of Preventive Care Services In Diabetic**

**Patients With And Without Depression**



(+): Presence of Depression

(-): Absence of Depression

Table 2.6: Results Of The Multivariable Logistic Regression: Effect Of Comorbid

Depression On The Receipt Of Diabetes Preventive Care Services.

Preventive Service	Depression Status	Sample Size	Crude Odds Ratios (95% CI)	Adjusted Odds Ratios (95% CI)	Adjusted For
A1C Testing	Non Depressed	3,460	1.00 (REF)	1.00 (REF)	Age, Gender, Race and Ethnicity Insulin use, Income level, Employment Status, Perceived health Status, BMI Status, Marital Status, Smoking Status, Primary Care Provider, Anemia, Back Disorders, Hyperlipidemia and Hypertension.
	Depressed	1,208	1.19 (1.01 – 1.44)	1.03 (0.83 – 1.28)	
Diabetic Foot Exam	Non Depressed	3,460	1.00 (REF)	1.00 (REF)	Age, Gender, Race and Ethnicity, Insulin Use, Perceived Health Status, Hyperlipidemia
	Depressed	1,208	1.20 (1.01 – 1.42)	1.12 (0.94 – 1.34)	
Lipid Check	Non Depressed	3,460	1.00 (REF)	1.00 (REF)	Age, Gender, Race and Ethnicity, Income Level, Insulin Use, Educational Status, Perceived Health Status, Smoking Status, Marital Status,, Primary Care Physician, Hyperlipidemia, and Headaches.
	Depressed	1,208	1.11 (0.94 – 1.32)	1.07 (0.88 – 1.30)	
Influenza Vaccination	Non Depressed	3,460	1.00 (REF)	1.00 (REF)	Age, Gender, Race and Ethnicity, Insulin Use, Income Level, Perceived Health Status, Educational Status, Employment Status, Smoking Status,, Primary Care Physician, Headaches, Back Disorders, Upper Respiratory Disorders, Hypertension, Hernia and Hyperlipidemia.
	Depressed	1,208	1.06 (0.88 – 1.28)	1.02 (0.83 – 1.25)	
Dilated Eye Exam	Non Depressed	3,460	1.00 (REF)	1.00 (REF)	Age, Gender, Race and Ethnicity, Income Status, Perceived Health Status, Educational Status, Employment Status, Insurance Status, Primary Care Provider, Marital Status, Hypertension, Hyperlipidemia and Back Disorders.
	Depressed	1,208	0.94 (0.79 – 1.11)	0.93 (0.76 – 1.12)	

Routine Medical Checkup	Non Depressed	3,460	1.00 (REF)	1.00 (REF)	Age, Gender, Race and Ethnicity, Income Status, Perceived Health Status, Educational Status, Employment Status, Back Disorders, Insurance Status, Primary Care Provider, Hypertension, Marital Status and Hyperlipidemia
	Depressed	1,208	0.80 (0.63 – 0.99)	0.81 (0.60 – 1.10)	

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## Manuscript 3

### Predictors And Costs Of Inpatient And Outpatient Visits For Hypoglycemia In Type 2 Diabetes

Publication status: In progress, planning on submitting to the American Journal Of Managed Care.

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Short Title: Association between Adherence and Hypoglycemia

Word length: 5,875 References: 62 Tables: 9 Figures: 3

Short Title Manuscript III: Predictors And Costs Of Hypoglycemia

### 3.1 Background

Hypoglycemia is a serious complication that is associated with the treatment of diabetes resulting in a significant burden to the patients with diabetes.<sup>166</sup> While most hypoglycemic events are mild and self-managed, more severe hypoglycemic events require medical assistance and result in the development of serious complications. It is well documented that despite the variations in severity, hypoglycemia is known to cause negative health outcomes including increased morbidity, decreased quality of life, and rare occurrences of mortality in patients with diabetes.<sup>167</sup> The most common symptoms associated with hypoglycemia include palpitations, trembling, sweating, hunger, and confusion.<sup>168</sup> Long-term consequences of hypoglycemia include weight gain, cardiovascular diseases, and coma.<sup>167</sup> Even though the symptoms and complications of diabetes differ among patients, a great degree of decline in cognitive and motor function as well as hormonal counter regulation has been previously documented.<sup>169</sup> The fear of severe hypoglycemia requiring clinical assistance can seriously compromise the self-management of diabetes thereby causing the patients to prefer sub-optimal blood glucose control over incidents of hypoglycemia.<sup>170</sup>

Though the estimates regarding the incidence of hypoglycemia in Type 2 Diabetes (T2DM) are varied, previous studies identify several factors associated with hypoglycemia.<sup>167,168,171-174</sup> For example antidiabetic medications, particularly insulin and sulfonylureas (SUs), are among the principal risk factors for developing hypoglycemic events.<sup>175-178</sup> This is concerning as intensive therapy with antidiabetic

drug agents is strongly associated with improvement in diabetes control including reducing the risk of developing micro- and macrovascular complications.<sup>95,179,180</sup> Similarly, many patient specific factors are also associated with the development of hypoglycemia. These factors include age and gender as well as physiological factors (e.g. chronic kidney disease and liver disease).<sup>177,181</sup> Lastly, certain behaviors like continuity of physical exercise, intake of food and consumption of alcohol also increase the risk of hypoglycemia.<sup>168,173</sup>

Apart from the clinical impact, hypoglycemia has also been shown to pose a significant financial burden to the patient as well as the health care system<sup>167,177,182</sup>. For example, Pelletier and colleagues estimated that the mean annual allowed charge for hypoglycemia was \$345 (2007 US dollars).<sup>183</sup> Similarly, Quilliam et al. estimated the rate and costs of hypoglycemia among working-age patients with type 2 diabetes and found the total hypoglycemia costs accounted for 1.0% of all inpatient costs, 2.7% of ED costs, and 0.3% of outpatient costs. The mean costs for hypoglycemia visits were estimated to be \$17,564 for an inpatient admission, \$1387 for an ED visit, and \$394 for an outpatient visit. The authors concluded that hypoglycemia was associated with higher costs as compared to other diabetic and non-diabetic costs.<sup>184</sup> These higher costs might be direct costs because of primary care visits, emergency room visits, hospitalizations etc. or indirect costs resulting from absence from work, disability, premature retirement and reduced productivity.<sup>185,186</sup>

The incidence and effects of hypoglycemia are more pronounced in insulin treated type 1 diabetes mellitus (T1DM). Hence, though the predictors and costs of hypoglycemia have been well outlined for T1DM, there is a paucity of research regarding the factors that cause hypoglycemia specifically in patients with type 2 diabetes mellitus (T2DM). Moreover, due to the varied definitions of hypoglycemia operationalized in various studies and other methodological differences, findings from these studies often lack generalizability. As the incidence rates of people suffering from diabetes will almost double by 2050, <sup>2</sup> more research on this devastating complication of antidiabetic treatment is warranted. Hypoglycemic events will continue to place a greater strain on the health care costs and resources.

To expand on previously published studies, we conducted a cross sectional study of persons with T2DM using an insurance claims database to identify predictors and outline the costs of hypoglycemia treated in an outpatient or inpatient setting.

### *3.2 Methods*

#### *3.2.1 Datasource*

For the purpose of our study, we used the Blue Cross and Blue Shield Of Rhode Island (BCBSRI) administrative claims data for the years 2009 - 2012. BCBSRI is a non-profit hospital service and medical service corporation covering more than 600,000 members. In the data extract used for our analyses, all the members had at least one International Classification of Disease-9 (ICD-9) code for diabetes (ICD-9 250.XX) between 2009 and 2012. To achieve the aims of our study, we utilized three administrative files, including: eligibility files, medical claims (inpatient and outpatient) and pharmacy claims. The enrollment file included age, gender as well as the start and end dates for enrollment in the health plan. Similarly, the outpatient and inpatient files include diagnosis information (ICD-9 codes), Current Procedural Terminology (CPT) codes, admit and discharge dates as well as cost and copayment information. The medication claims dataset included prescription medications dispensed during the study period and included the National Drug Codes (NDC), drug product names, prescription quantity (number of units dispensed) and days supplied at the time of dispensing (e.g. 30 day supply of medication). Due to the comprehensive nature of the claims provided in the dataset, it can be assumed that this dataset provides a near complete picture of an individual's health care.



### *3.2.2 Research design and study population*

Using the medical claims, inpatient and outpatient, as well as prescription claims, we conducted a cross sectional study. All the patients included in the dataset had a diagnosis of diabetes. As our interest was in factors associated with hypoglycemia in T2DM, we further excluded patients who had at least one claim for type 1 diabetes (ICD-9 250.X1 or 250.X3) or gestational diabetes (ICD-9-CM 648).

### *3.2.3 Identification of Hypoglycemia*

The principal objective of our study was to identify independent predictors of hypoglycemia in T2DM. In order to identify hypoglycemia in the inpatient and outpatient medical settings, we used an algorithm designed by Ginde and colleagues<sup>187</sup>. Within this algorithm, specific codes related to hypoglycemia (251.0 251.1 251.2 270.3 775.0 775.6 962.3) are first directly classified as a hypoglycemic event. Secondly, additional instances of hypoglycemia are identified using ICD- 9 code of 250.8 in the absence of other contributing diagnoses (ICD -9 259.8, 272.7, 681.XX, 682.XX, 686.9X, 707.1-707.9, 709.3, 730.0-730.2, or 731.8). This algorithm is well validated and demonstrated a positive predictive value of 89% for detecting hypoglycemia visits.<sup>187</sup> As all episodes of hypoglycemia identified in our study required medical intervention, we considered these events as serious and thus will utilize this terminology in the presentation of our results. Using this information, we

created two groups, those with at least one serious hypoglycemic event (n=1243) and those who did not have a serious hypoglycemic event (n=28,128).

#### *2.4 Identification of Independent Predictors*

We assessed the relevant demographic characteristics of the sample population including age (18-34, 35-49, 50-64, 65 and above) and gender. We used the Charlson's Comorbidity Index in order to examine the composite impact of the burden of comorbid diseases on the risk of having a hypoglycemic event. In addition, we also defined the prevalence of specific individual comorbidities predictors of hypoglycemia using the Elixhauser Comorbidity Index. Previous studies have identified other diabetes micro- and macrovascular complications that might be predictive of hypoglycemia in patients. We also identified the presence of these complications as well as other diseases like influenza and pneumonia, which can potentially to increase the likelihood of a hypoglycemic event.<sup>183,188,189</sup> In case of an overlap of the conditions, we considered the condition defined under one set of comorbidities preferably in the order of elixhauser comorbidity index, micro and macrovascular complications and other diseases.

#### *3.2.5 Characterizing The Use Of Medications*

We use a combination of National Drug Codes (NDC) and drug product names in order to identify the use of both diabetic and non-diabetic medications that might have an association with the incidence of hypoglycemia. Among the antidiabetic medications, we specifically identified the use of all the major classes of oral

antidiabetic medications including biguanides, sulfonylureas (SUs),  $\alpha$ -glucosidase inhibitors, DPP-4 inhibitors (DPP), meglitinides, thiazolidinediones (TZDs) as well as insulin. With respect to the other medications, we identified use of other medications previously suggested to cause hypoglycemia: angiotensin-converting enzyme (ACE) inhibitors, allopurinol, angiotensin II receptor blockers (ARBs), benzodiazepines,  $\beta$ -blockers, fibrates, fluoroquinolones, nonsteroidal antiinflammatory drugs (NSAIDs), trimethoprim, and warfarin.<sup>173,190-192</sup>

### *3.2.6 Estimating Costs*

In order to examine the medical costs for hypoglycemia, we used the total allowed amount paid for the services for both inpatient and outpatient encounters. In addition to the measurement of total costs, we also stratified the costs into 3 mutually exclusive groups namely costs related to hypoglycemia as identified using the Ginde algorithm;<sup>187</sup> costs related to other diabetes-related claims as identified by primary ICD-9 250.XX); and costs related to all other claims. We classified all the episodes occurring on the same day as a single episode of care. All the costs were adjusted to 2012 equivalents (final year of available data) using the regional Consumer Price Index medical care expenditure category in order to make accurate comparison of costs across all study years.

### *3.2.7 Statistical Analyses*

We created two groups for comparison in our study, those with a serious hypoglycemic event and those without. We compared the prevalence of the selected

covariates among the patients with or without any hypoglycemic events by examining the frequencies and thereafter using the Cochran-Mantel-Haenszel statistic for categorical variables and Student's t-test for continuous variables. We then selected all the variables with a p-value of less than 0.25 in these preliminary bivariate analyses. We then developed a predictive logistic regression model using the variables identified in the above process, initially fitting a preliminary model containing all of the above variables and then further refining it using a manual iterative process of refinement. During this process, we sequentially excluded variables that were not contributing significantly to the model (Wald p-value >0.10) and thus were potentially not associated with hypoglycemia. Further, we carried out likelihood ratio testing in order to confirm the exclusion. After identifying a working model with all of the relevant predictors included, we further assessed multicollinearity in the model. For this purpose, we used the variation inflation factor (VIF), and Eigen values to make the decisions on exclusion of collinear variables. These were calculated utilizing a separate regression model and specifically using the VIF, TOL, and Collin options. If two variables were found collinear, we included the variable that was clinically more relevant to our analysis. We tested all two-way interactions between the independent variables in a stepwise process that was similar to the one used to in order to build the initial model (using likelihood ratio testing for confirmation). We retained each interaction term if it was significant and continued this process until all interaction terms were either removed from the model, or retained if found significant. We used AIC (the Akaike Information

Criterion) and Hosmer-Lemeshow test to assess goodness of fit at all steps of building the final model. At the end of this process we then reported multivariable (adjusted) odds ratios (AORs), including their respective 95% confidence intervals (95% CI). For the cost analyses, we conducted Student t-tests to compare mean costs across the created cost subgroups. All statistical tests were conducted with a 2-tailed alpha of 0.05. All analyses were performed using SAS software version 9.3 (SAS Institute Inc., Cary, NC). This study was reviewed and approved as exempt by the University of Rhode Island's Institutional Review Board.

### 3.3 Results

#### 3.3.1 Demographics

The initial dataset of patients with diabetes was comprised of 36,954 individuals identified as having diabetes (ICD-9 250.xx). After excluding the patients with type 1 diabetes or gestational diabetes (n=7,240) as well as patients below the age of 18 (n=343), our final analytic sample included 29,371 patients with T2DM. Among the eligible sample, 1,243 (4.2%) patients experienced a serious hypoglycemic event over the three-year period while 28,128 (95.7%) patients did not have any reported hypoglycemic events. The demographic characteristics of the study sample stratified by the presence of serious hypoglycemia are described in Table 3.1. Overall, the mean age was 61.4 years and was slightly higher in the patients with serious hypoglycemic events as compared to those who did not (65.3 Vs 61.2, respectively). When divided into specific age groups, it could be seen that that 46.7% (580 patients) of the hypoglycemic group had an age above 65 years in comparison to the 9,716 patients(46.7%) in the non-hypoglycemic group ( $\chi^2$ : 80.62, p-value: <0.001). Moreover, the observed gender distribution was similar across both groups with the proportion of females being lower in both hypoglycemic (567 patients, 45.6%) and non-hypoglycemic groups (13,275 patients, 47.2%)

#### 3.3.2 Clinical Characteristics

Comparison of clinical characteristics in patients with or without serious hypoglycemia revealed a higher prevalence of comorbidities in the hypoglycemic

group (Table 3.2). Overall, the Charlson's comorbidity score describing the burden of other diseases was found to be higher in the hypoglycemic group (mean = 2.97 +/- 1.18) than the non-hypoglycemic group (mean=2.15 +/- 1.20; t=36.22; p value <0.001). When divided into separate groups, it was found that 250 patients in the hypoglycemic group (20.1%) and 12,690 patients in the non-hypoglycemic group (45.1%) had a score of 0 indicating a higher percentage of patients in the non-hypoglycemic group did not suffer from any comorbidities. In contrast, 607 patients in the hypoglycemic group (48.8%) and 6,160 patients from the non-hypoglycemic group (21.9%) had a score of greater than 3, indicating a greater proportion of patients in the hypoglycemic group suffering a higher burden of comorbidities ( $\chi^2=566.30$ ; p-value: <0.001). Table 3.3 also provides more detail on individual comorbidities (as identified using the Elixhauser Comorbidity Index).<sup>193</sup> The most commonly observed comorbidities had a higher prevalence in the hypoglycemic group as opposed to the non-hypoglycemic group. For example, congestive heart failure (28.3% vs 8.0%,  $\chi^2$ : 353.31, P value <0.001), cardiac arrhythmias (26% vs 13%,  $\chi^2$ : 170.5, p value: <0.001), valvular disease (13.4% vs 7.4%,  $\chi^2$ : 60.79,  $\chi^2$ : 60.79 p value <0.001), peripheral vascular disorders (27.8% vs 11.6%,  $\chi^2$ : 289.3, p value: <0.001), hypertension uncomplicated (61.85%), chronic pulmonary disease (66.3% vs 61.6%,  $\chi^2$ : 11.24, p value: 0.0008), hypothyroidism (16.7% vs 13.3%,  $\chi^2$ : 11.43, p value: 0.0007), solid tumor without metastasis (16.0% vs 10.5%,  $\chi^2$ : 36.22, p value: <0.001) and depression (19.7% vs 13.7%,  $\chi^2$ : 2339.59, p value: <0.001). Some of the least frequent comorbidities also displayed a higher prevalence in the hypoglycemic

group. For example, paralysis (1.7% vs 0.4%,  $\chi^2$ : 43.03, p value <0.001), peptic ulcer disease excluding bleeding (1.5% vs 0.7%,  $\chi^2$ : 9.28 p value : 0.002), lymphoma (1.7% vs 0.9%,  $\chi^2$ : 7.83 p value: 0.005) and metastatic cancer (2.9% vs 1.3%,  $\chi^2$ : 20.86, p value: <0.001). Moreover, as seen in table 3.4 the most prevalent macrovascular and microvascular complications of diabetes demonstrated higher prevalence in the hypoglycemic group. . For instance coronary artery disease (33.0% vs 18.7%,  $\chi^2$ : 156.77, p value: <0.001), arrhythmias (15.7% vs 7.1%,  $\chi^2$ : 126.45, p value: <0.001), stroke (7.5% vs 2.2,  $\chi^2$ : 98.32, p value: <0.001) peripheral vascular disease (36.2% vs 15.4%,  $\chi^2$ : 380.37, p value: <0.001), diabetic retinopathy (20.8% vs 13.7%,  $\chi^2$ : 49.9, p value <0.001), diabetic neuropathy (5.7% vs 2.0%,  $\chi^2$ : 74.7, p value: <0.001) and ulcers (27.2% vs 5.3%,  $\chi^2$ : 969.8, p value: <0.001) were all observed to a higher degree in the hypoglycemic group. Among the other diseases that might contribute to the increased likelihood of having a hypoglycemic event, liver disorders (6.6% vs 4.3%,  $\chi^2$ : 14.07, p value: 0.0002) were highly prevalent while Addison's disease (1% vs 0.1%,  $\chi^2$ : 38.13, p value: <0.001) were rarely observed. The presence of these comorbidities was also significantly higher in the patients who had any events of hypoglycemia.

### *3.3.3 Use of Medications*

The mean number of medications (SD) taken was higher in the patients in the hypoglycemic group (mean=15.31 +/- 12.21) as compared to those in the non-hypoglycemic group (mean=10.97 +/- 9.63; t=56.78; p value 0.001). We further



assessed the use of diabetes and non-diabetes medications (Tables 3.5 - 3.7). Overall, the use of diabetic medications was common. Moreover, the use of these medications was significantly higher in the hypoglycemic group as compared to the non-hypoglycemic group. Specifically, 2,873 (9.5%) patients were using insulin with the use being significantly higher in the hypoglycemic group as compared to the non-hypoglycemic group (24.14% vs 9.14%;  $\chi^2= 303.24$ ; p-value: <0.001). The use of metformin (42.8%) was found to be high within the overall sample but comparable in the hypoglycemic and non-hypoglycemic groups (42.5% vs 42.8%). Furthermore, 7,821 patients (26.6%), 2,881 patients (9.8%) and 2,458 (8.4%) patients were being prescribed sulfonylureas, TZDs and DPP respectively with the use being higher in patients in the hypoglycemic group. More specifically, use of sulfonylureas (41.5% vs 26.0%;  $\chi^2=147.17$ ; p-value: <0.001), TZDs (11.6% vs 9.7%;  $\chi^2=4.62$ ; p value: 0.03) and DPP-4 (9.7% vs 8.3%;  $\chi^2=2.79$ ; p value: 0.09) were more prevalent in those with serious hypoglycemia compared to those without. The use of other classes of diabetic medications like alpha glucosidase inhibitors (0.3%) and meglitinides (0.9%) was relatively rare and comparable in the hypoglycemic and non-hypoglycemic groups. Overall, it can be seen from Table 3.5 that 34.9% of the hypoglycemic group and 46.8% of the non-hypoglycemic group were not taking antidiabetic medication.

Similarly, as seen in Table 3.6, the prevalence of use of non-diabetic medications was also significantly higher in the hypoglycemic group as compared to the non-hypoglycemic group. Furthermore, 11,097 patients and 7,888 patients were prescribed ACE inhibitors (44.2% in hypoglycemic group and 37.5% in non-

hypoglycemic group;  $\chi^2=22.51$ ; p value:  $<0.001$ ) and beta-blockers (38.9% in hypoglycemic group and 26.3% in non-hypoglycemic group;  $\chi^2=96.44$ ; p value:  $<0.001$ ). Use of ARBs was more comparable between the two groups) 9.7% in hypoglycemia group versus 8.6% in non-hypoglycemia group). In contrast, use of other medications was much more common in those with hypoglycemia than those without hypoglycemia. For example warfarin (12.71% in hypoglycemic group and 5.40% in non-hypoglycemic group;  $\chi^2=118$ ; p value:  $<0.001$ ), fluoroquinolones (33.1% in hypoglycemic group and 21.8% in non-hypoglycemic group;  $\chi^2=87.37$ ; p value:  $<0.001$ ), fibrates (8.6% in hypoglycemic group and 7.6% in non-hypoglycemic group;  $\chi^2=1.61$ ; p value: 0.20) and NSAIDs (27.7% in hypoglycemic group and 28.5% in non-hypoglycemic group;  $\chi^2=0.37$ ; p value: 0.53). Use of other evaluated agents was similar between the two groups and is presented in Table 3.6.

### *3.3.4 Results Of Multivariable Logistic Regression*

The results of the multivariable logistic regression analyses are presented in Table 3.7. While using the age group of 18 – 34 years as our reference, it was seen that with increasing age the relative likelihood of hypoglycemia generally decreased. For example, the AOR of patients aged 35 – 49 years was 22% lower (AOR 0.78; 95% CI 0.51 to 1.18) while the AOR for patients aged 50 – 64 years decreased by 24% (AOR 0.76; 95% CI 0.78 to 0.85). The lowest risk of a hypoglycemic event was found in the patients who were aged 65 or above (AOR 0.71; 95% CI 0.47 to 1.07). With respect to

gender, it could be seen that both male enrollees had a 4% higher but statistically insignificant relative rate of hypoglycemia (AOR 1.04; 95% CI 0.92 to 1.18).

For other factors, there was an increased likelihood of severe hypoglycemia in patients with higher overall burden of disease as measured by the Charlson's comorbidity index. As compared to patients with a comorbidity score of 0, patients with a comorbidity score of 1 were 38% (AOR 1.67; 95% CI 1.01 to 2.78) more likely to have a serious hypoglycemic event. Similarly, the relative risk of a serious hypoglycemic events in patients with a comorbidity score 2 (AOR 2.05; 95% CI 1.70) and those with a 3 or more (AOR 2.12; 95% CI 1.73 to 2.59) were more than twice that of patients with a comorbidity score of 0. In addition, presence of any claims for congestive heart failure (AOR 1.24; 95% CI 1.04 to 1.49), peripheral vascular disorders (AOR 1.19; 95% CI 1.02 to 1.40), paralysis (AOR 1.67; 95% CI 1.01 to 2.78), neurological disorders (AOR 1.52; 95% CI 1.22 to 1.89), obesity (AOR 1.30; 95% CI 1.01 to 1.67), fluid and electrolyte disorders (AOR 1.31; 95% CI 1.09 to 1.57), deficiency anemia (AOR 1.37; 95% CI 1.13 to 1.67) and psychoses (AOR 1.60; 95% CI 1.19 to 2.14) was associated with a higher relative rate of any serious hypoglycemic events. Among other macro-and microvascular complications of diabetes, claims for acute renal failure (AOR 1.67; 95% CI 1.01 to 2.78), ulcers (AOR 4.07; 95% CI 3.50 to 4.72), amputations (AOR 2.73; 95% CI 1.26 to 5.91) and Addison's disease (AOR 3.17; 95% CI 1.64 to 6.14) displayed a significantly higher relative risk of hypoglycemia. In contrast, patients who suffered from hypertension demonstrated a 16% reduction in the relative rate for hypoglycemia events (AOR 0.84; 95% CI 0.74 to 0.97).

While evaluating the effect of medication use on the likelihood of hypoglycemic episodes, it was seen that patients who were using 4-7 unique drugs were least likely to suffer any hypoglycemic event (AOR 0.48; 95% CI 0.36 to 0.64). Similarly, patients using between 8 – 10 medications (AOR 0.59; 95% CI 0.44 to 0.80) as well as patients using more than 10 medications (AOR 0.66; 95% CI 0.56 to 0.79) had a 41% and 34% reduction in the risk of any hypoglycemia event. Most of the antidiabetic medications were associated with higher relative rates of hypoglycemia. Moreover, patients using insulin were more than twice as likely as those not using insulin to have any hypoglycemia related claims (AOR 2.20; 95% CI 1.88 to 2.56). Similarly, among the oral antidiabetic medications, sulfonylureas (AOR 1.71; 95% CI 1.49 to 1.97) and meglitinides (AOR 1.75; 95% CI 1.14 to 2.70) were associated with a 71% and 75% increased relative risk for a serious hypoglycemic events.

### *3.3.5 Results Of Cost Analyses*

Table 3.8 presents the results of the costs analyses. We estimated that 0.5% of inpatient encounters were associated with hypoglycemia. Moreover, 6.9% of the inpatient visits were for other diabetes related outcomes while the remaining 92.6% of the visits were recorded for non-diabetes related care. Hypoglycemia related visits accounted for 0.7% of the total inpatient costs while non-hypoglycemia related diabetes costs accounted for 1.4%. The mean cost for inpatient visits for hypoglycemia was \$1,514.60. In comparison, the mean cost for an inpatient visit for

non-hypoglycemia related diabetes outcomes and non-diabetes related outcomes was \$232.71 and \$1,171.60 respectively (p value <0.001). Similarly, hypoglycemia accounted for 0.2% of the total outpatient visits while non-hypoglycemia related outcomes and non-diabetes related outcomes were responsible for 14.4% and 54.4% of the outpatient visits respectively. In case of the outpatient visits, the estimated costs for hypoglycemia were 0.2% of the total costs while non-hypoglycemia related diabetes costs were 7.6% of the total outpatient costs. The mean cost of outpatient visits for hypoglycemia, non-hypoglycemia related diabetes outcomes and non-diabetes related outcomes were \$142.91, \$83.93 and \$182.63 respectively (p value <0.001).

### *3.4 Discussion*

Our cross sectional study sought to identify the principal predictors of serious hypoglycemia (requiring inpatient or outpatient medical intervention) and estimate the related costs. Within our analyses, we considered a range of demographic and clinical factors such as age, gender, comorbid diseases, as well as medication use as potential predictors in our analysis. Though there have been previous studies highlighting the risk factors for hypoglycemia in various settings (for example, solely in the emergency department), our results provide a comprehensive evaluation of serious hypoglycemic events requiring medical intervention. Our study adds to the valuable literature thereby providing greater insights into management of hypoglycemia and health care resource use in patients with diabetes.

Previous literature has found several clinical, physiological as well as drug related factors to have a significant impact on the rates of hypoglycemia in patients.<sup>190,194,195</sup>

Some of the important predictors that we identified in our study were comorbidities including congestive heart failure, peripheral vascular disorders, hypertension, paralysis, neurological disorders, obesity, fluid and electrolyte disorders, anemia, psychoses, acute renal failure, ulcers, amputations, Addison's disease as well as a combined Charlson's comorbidity score. For example, in a case control study to analyze the clinical characteristics as well as risk factors that might be associated with hypoglycemia in non-diabetic hospitalized older adults, Shilo et al. found that low

plasma albumin level, liver disease, malignancy, and congestive heart failure were significant predictors of hypoglycemia.<sup>196</sup> Similarly, Simeone et al., conducted a study to identify predictors of hypoglycemia-related emergency department and outpatient visits in patients with type 2 diabetes. They found that coronary artery disease (AOR 1.38; 95% CI 1.29 to 1.49), heart failure (AOR 1.70; 95% CI 1.49 to 1.93), peripheral vascular disease (AOR 1.80; 95% CI 1.60 to 2.02), arrhythmia (AOR 1.22; 95% CI 1.04 to 1.44), and stroke (AOR 1.81; 95% CI 1.41 to 2.32) were all significantly increasing the risk of a hypoglycemic event with ulcer demonstrating a 6 fold increase in the likelihood of hypoglycemia.<sup>173</sup> Similarly, renal failure has also been shown to have a significant association with incidence of hypoglycemia.<sup>197</sup> For example, Durán-Nah and colleagues attempted to identify risk factors associated with symptomatic hypoglycemia and found a threefold increase in the rate of hypoglycemia in patients suffering from renal failure (AOR 3.0; 95% CI 1.20 to 7.70).<sup>198</sup> Furthermore, our findings are also consistent with other studies, which have previously identified various macrovascular, microvascular, as well as other comorbidities as important risk factors for hypoglycemia.<sup>166,169,199,200</sup> Our results were in contrast with some studies that have previously found a protective effect with an increase in the Body Mass Index (BMI).<sup>172,197,201</sup> For example, while exploring the potential determinants for severe hypoglycemia 10,251 participants, Miller et al. found that BMI of 30 or higher resulted in a 35% reduction of hypoglycemia as compared to a BMI of less than 25 (Hazard Ratio[HR] 0.65, 95% CI 0.5 to 0.85). Possible reasons for this might be poor nutrition as well as irregular food intake.

With respect to other patient level factors like age, gender as well as certain comorbidities, we found that there was no significant association with the incidence of hypoglycemia. There has been contrasting evidence in literature regarding the risk of hypoglycemia associated with these factors. Age has been previously demonstrated to be a significant predictor of hypoglycemia. For example, the ACCORD and ADVANCE trials reported a 3% and 5% increase in risk for hypoglycemia with each additional year of age, respectively.<sup>178,200-203</sup> Previous research suggests that along with the physiological changes that occur in the body with advancing age, other mechanisms that might contribute to incidence of hypoglycemia include decreased hypoglycemia awareness as well as decreased counter regulatory response to low blood glucose.<sup>175,204</sup> However, in contrast some studies hypothesize age to have a protective effect with the risk of hypoglycemia decreasing with increasing age.<sup>173,198</sup> Other studies demonstrate no association between age and hypoglycemia.<sup>166,205</sup> In our study, we found a clinically significant (but non-statistically significant) trend towards a protective effect. While evaluating gender as a predictor, there have been conflicting results in literature. For example, studies including the ADVANCE trial demonstrated no significant association between gender and the likelihood of hypoglycemia.<sup>166,197,201</sup> On the other hand, the ACCORD trial, demonstrated a higher risk of a hypoglycemic event for women (Hazard Ratio= 1.21, 95% CI 1.02 to 1.43).<sup>200</sup> Some observational studies have provided evidence of a lower rate of hypoglycemia in females as compared to males.<sup>173,205</sup> A possible explanation that is postulated for this gender variation in the incidence of



hypoglycemia is that even though women are more likely to use health care resources to a higher degree, it might be a result of a higher morbidity rate compared with men.<sup>206</sup> On the other hand there are known physiological differences between males and females with a known relative reduction of counter regulatory responses in females that might also contribute to the incidence of hypoglycemia.<sup>173,207</sup>

There has been considerable evidence that various treatment modalities might result in a higher propensity to suffer from hypoglycemia through various mechanisms like increase in insulin sensitivity.<sup>208</sup> In our study, we found that a higher number of medications used by the patient increased the risk of hypoglycemia. This finding is corroborated by other studies, which provided similar evidence regarding polypharmacy.<sup>209,210</sup> For example, Shorr et al in a study of 19,932 Tennessee Medicaid enrollees, aged 65 years or older found that patients using drugs from 5 or more therapeutic classes had a 30% increase in the likelihood of having a hypoglycemic event.<sup>211</sup> With respect to oral antidiabetic medications, we found a significantly increased risk with insulin, sulfonylureas and meglitinides. Even though tight glycemic control is being increasingly recommended in clinical practice, this has shown to pre-dispose patients to an increased risk of hypoglycemia.<sup>208</sup> For example, a prospectively planned group-level meta-analysis of various largescale trials demonstrated a two-fold increase in the risk of developing severe hypoglycemia in patients who were underwent intensive glucose lowering therapy.<sup>212</sup> Similarly, both prospective trials and retrospective studies have consistently demonstrated the higher risk of hypoglycemia events with insulin.<sup>169,199,213-215</sup> This risk however varies

with the patient's medication regimen as well as the severity of the person's diabetes.<sup>190</sup> However, fear of hypoglycemia is known to prolong the initiation of insulin therapy in patients thereby seriously compromising the achievement of glycemic goals.<sup>216</sup> Similarly, sulfonylureas have also traditionally been associated with an additional risk of hypoglycemia.<sup>169,190,215,217</sup> For example, Bodmer et al. conducted a nested case control study to compare the risk of lactic acidosis and hypoglycemia among patients with type 2 diabetes using oral antidiabetic drugs and found that sulfonylureas had a substantially higher risk of causing hypoglycemia (AOR 2.79 95% CI 2.23–3.50).<sup>197</sup> Literature suggests that meglitinides have a lower potential to cause hypoglycemia as compared to insulin and sulfonylureas.<sup>94</sup> Interestingly, we found no significant association between the biguanide class of medications and incidence of hypoglycemia. There has been prior evidence of these drugs having a reduced hypoglycemic effect and hence are usually used as first line therapy. We did not find any association between the use of non-diabetic medications like allopurinol, warfarin, fibrates, NSAIDs, or B-blockers with severe hypoglycemia in multivariate analyses. The use drugs have previously shown an increase the likelihood of incidence of hypoglycemia.<sup>166,190,218</sup>

Moreover, incidence of hypoglycemia has been associated with significant health care resource use as well as direct and indirect economic burden in previous literature.<sup>184,208,219,220</sup> Due to under reporting of hypoglycemia itself, these cost estimates are often underestimated. In our study, hypoglycemia related visits were accountable for 0.7% and 0.2% of the total costs for inpatient and outpatient visits

respectively. Our results might differ from results described in other studies due to variations in the methods to measure costs as well as definitions of hypoglycemia. For example, we calculated the cost estimates based on total amount that was paid for the services, which included the copay amounts. Heaton et al. in a study to determine the incidence and economic cost of hypoglycemia in patients with diabetes taking insulin found that mean cost per episode was \$1,186 (range, \$181-\$4,924) or \$7.04 per patient per month.<sup>221</sup> On the other hand, Quilliam et al. while investigating the incidence rate and costs of hypoglycemia in patients with T2DM estimated the mean costs per encounter for inpatient and outpatient visits for hypoglycemia to be \$17,564.25 and \$ 393.64 respectively.<sup>184</sup> Similarly, in a series of studies conducted in three European countries, the average cost per hypoglycemic event was found to be €537–688.<sup>222,223</sup> It was interesting to note that most of the hypoglycemia cost studies have been performed in patients who are being treated with insulin with there being a scarcity of information on patients who are being treated with non-insulin therapies.

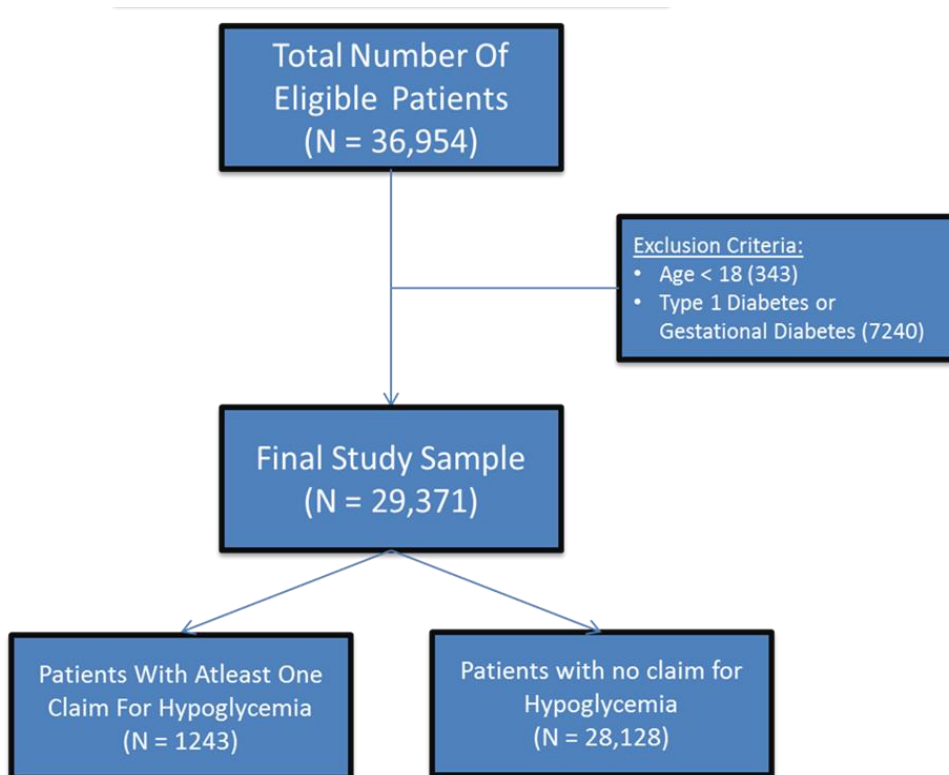
Even though, the study provides valuable insights into the predictors and costs of hypoglycemia in inpatient and outpatient settings, there are some inherent limitations to our study. Since our data represents a regional health plan, the results might not be generalizable to all patients with T2DM. Secondly, as with other studies, our diagnoses of hypoglycemia only represents the most severe cases for which medical assistance was necessary since only these may be considered as reliable events.<sup>174,190,224</sup> The true rates of hypoglycemia may be considerably higher than our

estimates. Moreover, we could not elucidate the effects of certain clinical as demographic aspects like blood glucose levels and race/ethnicity that are vital in the progression of diabetes. Lastly, due to the cross sectional design of the study, consideration of previous hypoglycemic events was beyond the scope of the study.

### *3.5 Conclusions*

Hypoglycemia is the principal and often underreported limiting factor in the management of patients with T2DM. Considering the clinical and economic implications of hypoglycemia, we conducted a cross sectional study to identify the predictors and estimate the costs of a comprehensive definition of severe hypoglycemia. Our study confirms that specific comorbidities as well as diabetic and non-diabetic treatment modalities are significantly predictive of hypoglycemic episodes. The cost estimates also provide evidence of the significant economic burden associated with hypoglycemia. The inpatient episodes related to hypoglycemia incur a much larger financial burden as compared to the outpatient episodes of hypoglycemia. Considering the clinical burden of hypoglycemia, reducing the incidence of this adverse event in diabetic patients will have a significant impact on improvement of the quality of life of patients.

**Figure 3.1 : Final Patient Selection Flowchart**



**Table 3.1: Demographic Characteristics of the study population Stratified by the Hypoglycemia**

Demographic Characteristic	Hypoglycemia (n=1243)(%)	No Hypoglycemia (n=28,128)(%)	Chi-Sq Value	P Value
<u>Age<sup>a</sup></u>				
18 - 34	29 (2.33)	808 (2.87)	80.62	<0.001*
35 - 49	137 (11.02)	4,469 (15.89)		
50 - 64	497 (37.38)	13,135 (46.70)		
65 And Above	580 (46.66)	9,716 (34.54)		
<u>Gender<sup>a</sup></u>				
Male	676 (54.38)	13,275 (47.19)	49.86	0.27
Female	567 (45.62)	14,853 (52.81)		
a: The Cochran-Mantel-Haenszel statistic was used to compare categorical variables. *: Significant at p value 0.05				

**Table 3.2: Prevalence of Comorbidities as Measured by the Charlson Comorbidity Index Stratified by the Presence of Serious Hypoglycemic Events**

Demographic Characteristic	Hypoglycemia (n=1243)	No Hypoglycemia (n=28,128)	Test Statistic Value	P Value
<b>Charlson's Comorbidity Index (Categorical Variable)<sup>a</sup></b>				
Cat 1 (0) <sup>+</sup>	250 (20.11)	12,690 (45.12)	529.82	<0.001*
Cat 2 (1) <sup>+</sup>	136 (10.94)	4,409 (15.67)		
Cat 3 (2) <sup>+</sup>	250 (20.11)	4,869 (17.31)		
Cat 4 (3 and above) <sup>+</sup>	607 (48.83)	6,160 (21.90)		
<b>Charlson's Comorbidity Index (Continous Variable)<sup>b</sup></b>				
Score	3.14 ± (2.86)	1.50 ± (2.03)	36.22	<0.001
<p><sup>+</sup>: Category (Score).  <sup>a</sup>: n(%) &amp; the Cochran-Mantel-Haenszel statistic was used to compare categorical variables.  <sup>b</sup>: Mean ± (Standard Deviation) &amp; a paired t-test was used to compare continuous variables.  *: Significant at p value 0.05 as derived from Chi-square or T test.</p>				



**Table 3.3: Prevalence of Elixhauser Comorbidity Conditions Stratified by the Presence of Serious Hypoglycemic Events**

Elixhauser Comorbidity Index <sup>a</sup>	Hypoglycemia (n=1,243)	No Hypoglycemia (n = 28,128)	Chi-Sq. Value	P Value
AIDS/HIV	3 (0.24)	37 (0.13)	1.05	0.3043
Alcohol Abuse	28 (2.25)	361 (1.28)	8.55	0.0034*
Blood Loss Anemia	28 (2.25)	339 (1.21)	10.58	0.0011*
Cardiac Arrhythmias	324 (26.07)	3,682 (13.09)	170.15	<0.001*
Chronic Pulmonary Disease	326 (26.23)	5,092 (18.10)	52.22	<0.001*
Coagulopathy	56 (4.51)	532 (1.89)	41.45	<0.001*
Congestive Heart Failure	290 (23.33)	2253 (8.01)	353.31	<0.001*
Deficiency Anemia	156 (12.55)	1,607 (5.71)	98.62	<0.001*
Depression	245 (19.71)	3,853 (13.70)	35.84	<0.001*
Diabetes Complicated	1,034 (83.19)	6,317 (22.46)	2339.5	<0.001*
Diabetes Uncomplicated	1,121 (90.19)	25,172 (89.49)	0.61	0.4343
Drug Abuse	20 (1.61)	230 (0.82)	8.83	0.0030*
Fluid And Electrolyte Disorders	230 (18.50)	1191 (6.79)	241.52	<0.001*
Hypertension, Complicated	106 (8.53)	1190 (4.23)	52.11	<0.001*
Hypertension, Uncomplicated	825 (66.37)	17,341 (61.65)	11.24	0.0008*
Hypothyroidism	208 (16.73)	3,764 (13.38)	11.43	0.0007*
Liver Disease	114 (9.17)	1,732 (6.16)	18.35	<0.001*
Lymphoma	22 (1.77)	271 (0.96)	7.83	0.0051*
Solid tumor without metastasis	199 (16.01)	2,979 (10.59)	36.22	<0.001*
Metastatic Cancer	37 (2.98)	391 (1.39)	20.86	<0.001*
Obesity	79 (6.36)	1,388 (4.93)	5.06	0.0244*
Other Neurological Disorders	133 (10.70)	1,059 (3.76)	147.03	<0.001*
Paralysis	22 (1.77)	124 (0.44)	43.03	<0.001*
Peptic Ulcer Disease Excluding Bleeding	19 (1.53)	211 (0.75)	9.28	0.0023*
Peripheral Vascular Disorders	346 (27.84)	3,272 (11.63)	289.36	<0.001*
Psychoses	70 (5.63)	469 (1.67)	103.84	<0.001*
Pulmonary Circulation Disorders	65 (5.23)	700 (2.49)	35.24	<0.001*
Renal Failure	199 (16.21)	1,224 (4.35)	350.93	<0.001*
Rheumatoid Arthritis/ Collagen Vascular Diseases	87 (7.00)	1,284 (4.56)	15.85	<0.001*
Valvular Disease	167 (13.44)	2,087 (7.42)	60.79	<0.001*
Weight Loss	50 (4.02)	701 (2.49)	11.18	0.0008*

a: n(%) & the Cochran-Mantel-Haenszel statistic was used to compare categorical variables.  
 \*: Significant at p value 0.05 as derived from Chi-square

**Table 3.4: Prevalence of Micro and Macrovascular Diabetes Complications and Other Contributing Diseases Stratified by the Presence of Serious Hypoglycemic Events**

Diabetes Complications	Hypoglycemia (n=1,243)	No Hypoglycemia (n=28,128)	Chi Sq. Value	P value
Macrovascular				
Arrhythmia	196 (15.77)	2,016 (7.17)	126.45	<0.001*
Congestive Heart Failure	262 (21.08)	1,911 (6.79)	354.51	<0.001*
Coronary Artery Disease	411 (33.07)	5,269 (18.73)	156.77	<0.001*
Peripheral Vascular Disease	451 (36.28)	4,334 (15.41)	380.37	<0.001*
Stroke	94 (7.56)	765 (2.72)	98.32	<0.001*
Microvascular				
Acute Renal Failure	195 (15.69)	919 (3.27)	503.27	<0.001*
Amputation	9 (0.72)	61 (0.22)	12.87	0.0003 <sup>+</sup>
Chronic Renal Pathophysiology	131 (10.54)	951 (3.38)	171.89	<0.001*
Dialysis	7 (0.56)	66 (0.23)	5.18	0.0228 <sup>+</sup>
End Stage Renal Disease	3 (0.24)	12 (0.04)	9.24	0.0024 <sup>+</sup>
Diabetic Nephropathy	71 (5.71)	574 (2.04)	74.70	<0.001*
Diabetic Retinopathy	259 (20.84)	3,861 (13.73)	49.90	<0.001*
Ulcer	339 (27.27)	1,508 (5.36)	969.82	<0.001*
Other Contributing Diseases				
Addison's Disease	13 (1.05)	54 (0.19)	38.13	<0.001*
Liver Disease	82 (6.60)	1,225 (4.36)	14.07	0.0002*
Thyroid Disease	187 (15.04)	3,515 (12.50)	7.01	0.0081*

a: n(%) & the Cochran-Mantel-Haenszel statistic was used to compare categorical variables.  
\*: Significant at p value 0.05 as derived from Chi-square.  
+: Significant at p value 0.05 as derived from Fischer's Exact Test.

**Table 3.5: Concomitant Usage of Diabetic Medications Stratified by Exposure to Hypoglycemia**

Concomitant Medications <sup>a</sup>	Hypoglycemia (N = 1243)	No Hypoglycemia (N = 28,128)	Chi Sq.	P value
Alpha Glucosidase Inhibitors	9 (0.72)	80 (0.28)	7.61	0.0058 <sup>+</sup>
Biguanides	528 (42.48)	12,047 (42.83)	0.06	0.8065
Dipeptidyl Peptidase 4 Inhibitors	120 (9.65)	2,338 (8.31)	2.79	0.0945*
Insulin	300 (24.14)	2,572 (9.14)	303.24	<0.001*
Other Injectable Agents	32 (2.57)	504 (1.79)	4.06	0.0437*
Meglitinides	29 (2.33)	232 (0.82)	30.74	<0.001*
Sulfonylureas	516 (41.51)	7,305 (25.97)	147.17	<.001*
Thiazolidinediones	144 (11.58)	2,737 (9.73)	4.62	0.0315*

a: n (%) & the Cochran-Mantel-Haenszel statistic was used to compare categorical variables.  
 \*: Significant at p value 0.05 as derived from Chi-square.  
 +: Significant at p value 0.05 as derived from Fischer's Exact Test.

**Table 3.6: Prevalence of Anti-diabetic Medications Stratified by Exposure to Hypoglycemia**

Diabetes Medications	Hypoglycemia (N = 1,243)	No Hypoglycemia (N = 28,128)
No Therapy	434 (34.92)	13,175 (46.84)
<b>Monotherapy</b>		
Insulin	70 (5.63)	600 (2.13)
Sulfonylureas	102 (8.21)	1,192 (4.24)
Biguanides	112 (9.01)	4,641 (16.50)
Thiazolidinediones	6 (0.48)	233 (0.83)
AlphaglucoSIDase Inhibitors	3 (0.24)	10 (0.04)
Meglitinides	1 (0.08)	21 (0.07)
Dipeptidyl Peptidase – 4 Inhibitors	3 (0.24)	90 (0.32)
<b>Combination Therapy<sup>a,b</sup></b>		
Insulin + Biguanides	49 (3.24)	474 (1.69)
Insulin + Sulfonylureas	28 (2.25)	138 (0.49)
Insulin + Thiazolidinediones	8 (0.64)	58 (0.21)
Biguanides +Sulfonylureas	146 (11.25)	2,871 (10.21)
Biguanides + Thiazolidinediones	9 (0.72)	513 (1.82)
Sulfonylureas + Thiazolidinediones	11 (0.88)	188 (0.67)
Insulin + Biguanides + Sulfonylureas	57 (4.59)	498 (1.77)
Biguanides + Sulfonylureas + Dipeptidyl Peptidase – 4 Inhibitors	26 (2.09)	659 (2.34)
Biguanides +Sulfonylureas + Thiazolidinediones	32 (2.57)	651 (2.31)
Others	137 (11.02)	2,116 (7.52)
<p>a: n (%) &amp; the Cochran-Mantel-Haenszel statistic was used to compare categorical variables.  b: Examples of combination therapy (use of more than one medication) might include Glipizide/Metformin Hydrochloride, Glyburide/Metformin Hydrochloride, Pioglitazone Hydrochloride/Glimepiride, Pioglitazone Hydrochloride/Metformin Hydrochloride, Repaglinide/Metformin Hydrochloride, Rosiglitazone Maleate/Glimepiride, Rosiglitazone Maleate/Metformin Hydrochloride, Sitagliptin Phosphate/Metformin Hydrochloride.  *: Significant at p value 0.05 as derived from Chi-square.</p>		

**Table 3.7: Concomitant Usage of Non –Diabetic Medications Stratified by Exposure to Hypoglycemia**

Concomitant Medications	Hypoglycemia (N = 1243)	No Hypoglycemia (N = 28,128)	Chi Sq.	P-Value
<b>Overall Medication Frequency<sup>a</sup></b>				
Number of Medications	15.34 ± (12.21)	10.97 ± (9.63)		<0.001*
<b>Categorized Medication Frequency<sup>b</sup></b>				
Number of Medications				
0 - 3	296 (23.81)	7881 (28.02)	119.48	<0.001*
4 - 7	62 (4.99)	3347 (11.90)		
8 - 10	59 (4.75)	2255 (8.02)		
More than 10	826 (66.45)	14645 (52.07)		
<b>Medication Classes<sup>b</sup></b>				
ACE Inhibitors	549 (44.17)	10548 (37.50)	22.51	<0.001*
Allopurinol	70 (5.63)	1048 (3.73)	11.80	0.0006*
Angiotensin II Receptor Blockers	120 (9.65)	2419 (8.60)	1.67	0.1956*
Benzodiazepines	262 (21.08)	4815 (17.12)	13.05	0.0003*
Beta-Adrenergic Blocking Agents	484 (38.94)	7404 (26.32)	96.44	<0.001*
Fibrates	107 (8.61)	2146 (7.63)	1.61	0.2045*
Fluoroquinolones	411 (33.07)	6130 (21.79)	87.37	<0.001*
Nonsteroidal Anti-Inflammatory Drugs	344 (27.67)	8011 (28.48)	0.37	0.5379
Trimethoprim	4 (0.32)	92 (0.33)	0.01	0.9746
Warfarin	158 (12.71)	1520 (5.40)	118.01	<0.001*

a: Mean ± (STD. DEV) & T test used for continuous variables.  
b: n (%) & the Cochran-Mantel-Haenszel statistic was used to compare categorical variables.  
\*: Significant at p value 0.05 as derived from Chi-square.

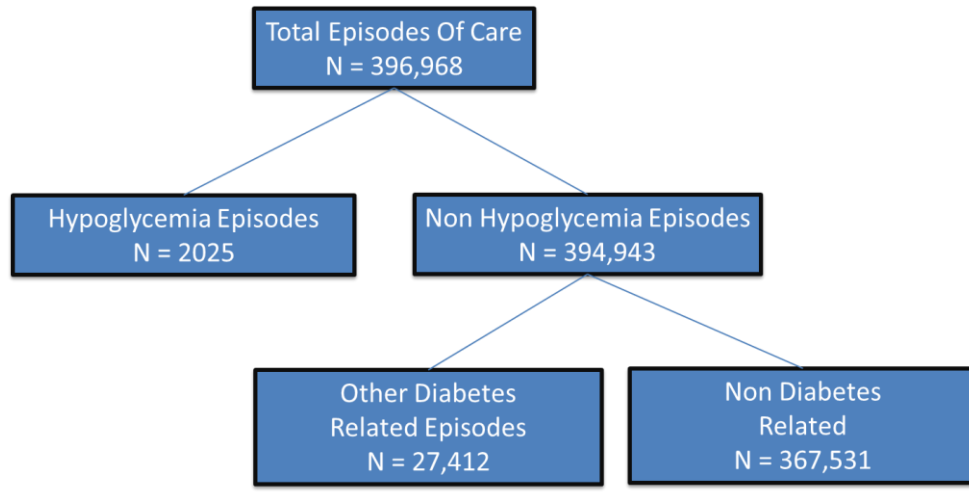
**Table 3.8: Independent Predictors Of Serious Hypoglycemic Events<sup>a</sup>**

Risk Factor	Crude OR	95% CI	Adjusted OR <sup>b</sup>	95% CI
Age Category				
18 - 34	1.00	NA	1.00	NA
35 - 49	0.85	0.56 – 1.28	0.78	0.51 – 1.18
50 - 64	1.05	0.72 – 1.54	0.76	0.50 – 1.13
65 And Above	1.66	1.13 – 2.43	0.71	0.47 – 1.07
Gender				
Female	1.00	NA	1.00	NA
Male	1.06	0.95 – 1.19	1.04	0.92 – 1.14
Charlson's Comorbidity Index				
CAT 1 (0)	1.00	NA	1.00	NA
CAT 2 (1)	1.56	1.26 – 1.93	1.38	1.11 – 1.72
CAT 3 (2)	2.60	2.18 – 3.11	2.05	1.70 – 2.47
CAT 4 (3 Or More)	5.00	4.30 – 5.18	2.12	1.73 – 2.59
Congestive heart failure <sup>c</sup>	3.49	3.04 – 4.01	1.24	1.04 – 1.49
Cardiac arrhythmia <sup>c</sup>	2.34	2.05 – 2.67	1.21	0.99 – 1.49
Peripheral vascular disorders <sup>c</sup>	2.93	2.57 – 3.33	1.19	1.02 – 1.40
Hypertension (uncomplicated) <sup>c</sup>	1.22	1.08 – 1.38	0.84	0.74 – 0.97
Paralysis <sup>c</sup>	4.10	2.59 – 6.48	1.67	1.01 – 2.78
Other Neurological Disorders <sup>c</sup>	3.06	2.53 – 3.70	1.52	1.22 – 1.89
Hypothyroidism <sup>c</sup>	1.30	1.11 – 1.51	1.13	0.96 – 1.34
Renal failure <sup>c</sup>	4.19	3.56 – 4.92	1.19	0.96 – 1.48
Obesity <sup>c</sup>	1.30	1.03 – 1.65	1.30	1.01 – 1.67
Fluid and electrolyte disorders <sup>c</sup>	3.11	2.68 – 3.62	1.31	1.09 – 1.57
Deficiency anemia <sup>c</sup>	2.36	1.98 – 2.82	1.37	1.13 – 1.67
Psychoses <sup>c</sup>	3.52	2.72 – 4.55	1.60	1.19 – 2.14
Chronic renal pathophysiology <sup>c</sup>	3.36	2.77 – 4.08	1.23	0.98 – 1.56
Acute renal failure <sup>c</sup>	5.50	4.66 – 6.50	1.79	1.44 – 2.23
Ulcer <sup>c</sup>	6.62	5.78 – 7.57	4.07	3.50 – 4.72
Amputation <sup>c</sup>	3.35	1.66 – 6.77	2.73	1.26 – 5.91
Addison's Disease <sup>c</sup>	5.49	2.99 – 10.09	3.17	1.64 – 6.14
Number Of Medications				
0 - 3	1.00	NA	1.00	NA
4 - 7	0.49	0.37 – 0.65	1.38	1.11 – 1.72
8 - 10	0.69	0.52 – 0.92	2.05	1.70 – 2.47
More than 10	1.50	1.31 – 1.72	2.12	1.73 – 2.59
Insulin <sup>c</sup>	3.16	2.75 – 3.62	2.20	1.88 – 2.56
Sulfonylureas <sup>c</sup>	2.02	1.80 – 2.27	1.71	1.49 – 1.97
Alphaglucosidase Inhibitors <sup>c</sup>	2.55	1.28 – 5.10	1.93	0.92 – 4.06

Meglitinides <sup>c</sup>	2.87	1.94 – 4.24	1.75	1.14 – 2.70
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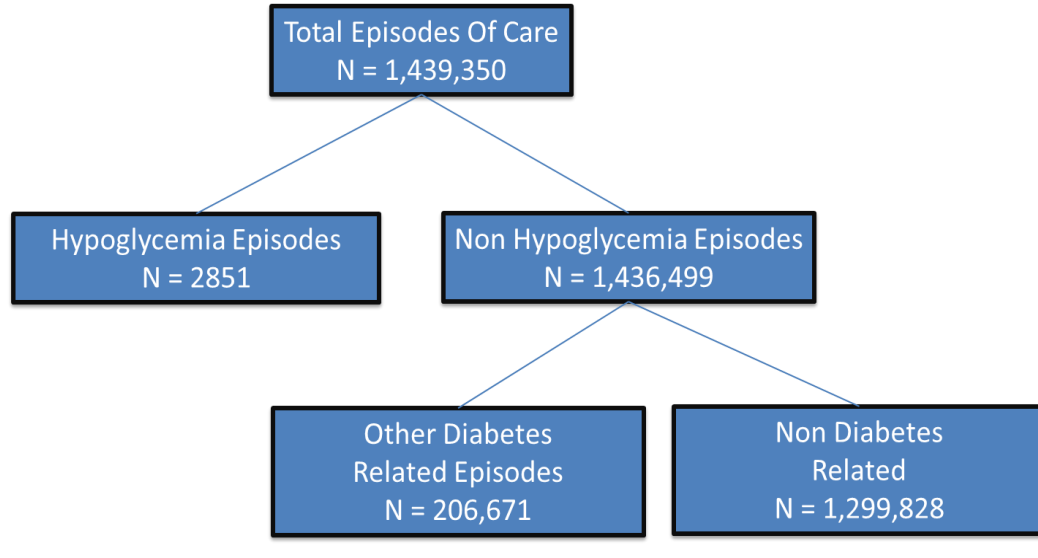
a: Independent predictors were identified using a conditional logistic regression model.  
b: Adjusted for all factors listed in the table.  
c: Dichotomized predictors; absence of factor is the referent group.

**Figure 3.2: Classification For Episodes Of Inpatient Claims**





**Figure 3.3: Classification Of Episodes For Outpatient Claims**



**Table 3.9: Cost Estimates of Hypoglycemic Events, Other Diabetes-Related Events, and All Other Events Stratified by Setting.**

Setting	Type Of Cost <sup>a</sup>	Encounters	Mean cost per encounter (\$)	Total Costs (\$) <sup>b</sup>
Inpatient Costs	Hypoglycemia	2,025	1,514.60	3,067,076
	Other Diabetes	27,412	232.71	6,379,256
	All Other	367,531	1,171.60	430,600,338
Total Inpatient Costs				440,046,671 <sup>c</sup>
Outpatient Costs	Hypoglycemia	2,851	142.91	407,456
	Other Diabetes	206,671	89.93	18,587,620
	All Other	1,229,828	182.63	224,610,691
Total Outpatient Costs				243,605,766 <sup>c</sup>
<p>a: Cost category identified using ICD-9 codes associated with the claim and creating 3 mutually exclusive groups:</p> <ol style="list-style-type: none"> <li>1) those identified as hypoglycemia (hypoglycemia costs).</li> <li>2) those with primary ICD-9 code 250.XX (other diabetes costs).</li> <li>3) others (all other costs).</li> </ol> <p>b: Total costs rounded to nearest dollar.</p> <p>c: Costs of hypoglycemic events, other diabetes-related events, and all other events may not sum to total costs due to rounding.</p>				

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## Manuscript 4

### Evaluating The Effects Of Hypoglycemic Episodes On The Persistence To Oral Sulfonylurea Therapy In T2DM

Publication status: In progress, planning on submitting to The Annals of Pharmacotherapy.

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Short Title: Association between Adherence and Hypoglycemia

Word length: 9,457 References: 89 Tables: 7 Figures: 4

Short Title Manuscript IV: Effect Of Hypoglycemia On Persistence

#### 4.1 Sulfonylureas

Sulfonylureas (SUs) have been the widely prescribed medications in the management of T2DM since the 1950s, with as many as 75 to 80% of patients initiated on one of these agents.<sup>225,226</sup> First-generation agents such as acetohexamide, chlorpropamide, and tolbutamide were very popular in the 1960s.<sup>227</sup> However, by the 1970s, many safety concerns arose over the use of these drugs with many observational studies and clinical trials, most notably the UGDP (University Group Diabetes Program), providing inconclusive evidence regarding the detrimental effects of this class of drugs.<sup>227</sup> The UGDP was an intervention trial of 1027 newly diagnosed T2DM patients with the objective of comparing the efficacy of oral anti hyperglycemic agents, insulin and diet alone in the prevention of diabetes-related vascular complications. This study demonstrated an annual rise of approximately 1% per year in the rate of cardiovascular mortality of patients receiving tolbutamide (a sulfonylurea) compared to diet alone. Subsequently, the safer second generation of SUs (e.g., glyburide, glipizide, and glimepiride) emerged in the next few decades and has largely replaced the first generation of SUs. Even though they differ from the first generation of SUs with respect to their chemical composition, both groups were found to be equivalent in their hypoglycemic effect.<sup>90</sup>



#### *4.1.1 Efficacy And Indications*

Many retrospective and prospective have focused on the efficacy of SUs. Although potency of effects can vary among patients, when used as a monotherapy in patients who cannot achieve the glycemic goals by nonpharmacologic interventions, SUs tend to lower A1C by 1.5 to 2.0 percentage points and fasting plasma glucose by 60 – 70 mg/dL, when used as monotherapy at maximal doses are used.<sup>90,228,229</sup> SUs can be used as the first line oral antidiabetic agents of choice in patients who fail to achieve adequate glycemic control using nonpharmacological measures or may also be added to a patients regimen if metformin monotherapy is contraindicated, not tolerated or does not achieve the target A1C at 3-6 months of treatment. SUs can be combined with other classes of OADs, excluding insulin secretagogues and combining daytime SUs with bedtime insulin, an increasingly popular practice lacking scientific evidence of potential advantages over insulin monotherapy, can help reduce can reduce insulin doses by half. SUs are preferred in patients who are not obese or overweight since weight gain is a major concern with this class of agents.<sup>227</sup> Similarly these drugs are used conservatively in the geriatric population as well as patients with impaired renal and hepatic functions and belong to pregnancy category B or C. However, according to the UKPDS, despite achieving the target achieved a A1C of <7 % in the first 3 years, only 34 % of patients attained a HbA1c <7 % at 6 years, with this number further declining to 24 % at 9 years.<sup>97,230</sup>

#### *4.1.2 Adverse Events With Sulfonylureas*

This class of drugs has been historically accepted as being well tolerated with only about 2 -5 % of patients reporting primary toxicities associated with it being hypoglycemia, weight gain, B cell exhaustion and adverse cardiovascular outcomes.<sup>231</sup>

Previous literature attributes initiation of SU therapy to a resulting increase in body weight, which also accompanies many of agents, apart from metformin, that are used for diabetes management.<sup>232</sup> Typically, various studies report a weight gain of approximately 1 – 4 kg.<sup>227,231-235</sup> There have been concerns regarding the cardiac safety of the sulfonylureas class of drugs especially after research on the physiological effect of these drugs.<sup>99,236-238</sup> SUs usually affect an initial increase in the B cell function, which is followed by a gradual and linear reduction, which goes hand in hand with the therapeutic failure of these drugs and the resulting progressive worsening of glycemic control.<sup>217,239,240</sup>

#### *4.1.3 Hypoglycemia with Sulfonylureas*

Even though different SUs possess different pharmacotherapeutic profiles, the major, most common, and potentially, the most worrisome adverse effect associated with this class of drugs is hypoglycemia. The risk of development of hypoglycemia episodes differs between different SUs with the likelihood of the prolonged manifestation of this side effect being greater with longer-acting agents like

chlorpropamide, glyburide, glibenclamide and longer acting glipizide as compared to the newer second generation like glimepiride (150 vs 105 episodes for glibenclamide and respectively).<sup>94,241,242</sup> Similarly, other factors like timing of the drug, dose, and potency of the specific agent are known to affect the risk of this adverse event. Previous studies have attempted to characterize the risk factors for hypoglycemia in patients with T2DM. Among the other patient related factors, advanced age, taking multiple medications, inconsistent frequency of meals and physical activities as well as impaired organ system functions are clearly known to increase the risk of recurrent hypoglycemic effects of SUs.<sup>243</sup> For example, Setzer et al., in a comprehensive review of 1,418 cases of severe drug-induced hypoglycemia, found that sulfonylurea ingestion was a factor in 65% of adult cases, 86% of cases were older than 50 years, and the omission of 1 or more meals was implicated in 80% of cases. Moreover these results should be viewed in light of the drawbacks of this study including lack of a control group, inclusion of patients with and without diabetes as well as intentional overdoses, and design flaws<sup>244</sup>. Similarly, Asplund et al reported that more than 90% of the 57 type 2 diabetic patients experiencing glibenclamide-associated hypoglycemia were older than 60 years and more than 70% were older than 70 years.<sup>245</sup>

Bonds and colleagues, in a secondary analysis of the ACCORD clinical trial data, did not find any association between sulfonylureas and severe hypoglycemia in both the intensive [Hazard ratio 1.06, 95% CI 0.88–1.28] and the standard intervention group [Hazard ratio 0.85, 95% CI 0.6–1.20].<sup>178</sup> Similarly, Burge et al. in a prospective,

randomized, double-blind clinical trial evaluated the hypoglycemic effects of maximum doses of once-daily second-generation sulfonylureas in the elderly patients. Each patient was assigned to either glyburide or glipizide therapy and took part in three 23-hour fasting studies after undergoing sequential administration of 1 week of placebo and 1 week of 10 mg and 1 week of 20 mg of the assigned sulfonylurea. It was observed that none of the 58 patients had an event of hypoglycemia during the fasting period.<sup>246</sup> Similarly, The GUIDE study which randomized 845 T2DM patients to gliclazide modified release (MR) or glimepiride monotherapy or in combination with other treatments to HbA1c and safety by episodes of hypoglycemia, showed no hypoglycemia requiring external assistance for similar HbA1c reduction in both groups, age notwithstanding.<sup>235</sup>

However, in contrast, many other clinical trials as well as observational studies implicate pharmacological effect of the SUs as the principal cause. Data from several clinical trials, though variable with respect to the rates of hypoglycemic events, attribute hypoglycemia to SU therapy. In the UKPDS, the rates of hypoglycemia varied from 11% to 17.7% depending on the specific agent used with the rates of severe episodes being less than 1% with either chlorpropamide or glibenclamide.<sup>97,232</sup>

However, failure to provide details of the diagnosis of the hypoglycemia episode and considerable inter changing between agents were the principal drawbacks of this study which made it difficult to define and associate the hypoglycemic episode to a particular agent.<sup>97</sup> However, in comparison to the Diabetes Control and Complications Trial (DCCT), the relative risk of hypoglycemia was much lower in the

UKPDS. Both, Draeger et al. and Clarke et al. compared glyburide with other sulfonylureas and found varying rates of hypoglycemia, with all the agents within the class associated with a higher risk of hypoglycemia.<sup>242,247</sup>

Gangji et al. in a meta-analysis to glyburide with other secretagogues as well as insulin with respect to the potency to cause hypoglycemia and cardiovascular events found a 52% and 83% greater risk of hypoglycemic events associated with glyburide in comparison to other secretagogues (Relative Risk (RR) 1.52 [95% CI 1.21-1.92]) and other sulfonylureas respectively ( RR 1.83 [95% CI 1.35-2.49]).<sup>243</sup> Hollander et al. compared the effects of nateglinide, glyburide, and placebo on post meal glucose excursions and insulin secretion in 152 patients and as one of the outcomes found that nateglinide-treated patients had significantly fewer hypoglycemia events as compared to those treated with glyburide but more events than placebo-treated patients (12 vs. 53 vs. 2, respectively).<sup>248</sup>

Van Staa et al. assessed the risk of hypoglycemia in 33,243 patients treated with sulfonylureas in 719 clinical practices in the UK and found that a diagnosis of hypoglycemia during sulfonylurea therapy was recorded in 605 people over 34,052 person-years of sulfonylurea therapy thus amounting an annual risk of 1.8%<sup>249,250</sup> while in another review in Germany, the incidence rates for severe hypoglycemia was 0.86/1000 person- therapy years and 5.6/1000 person-years for glimepiride and glibenclamide respectively.<sup>251</sup>

Jennings et al. demonstrated that up to 20% of the patients taking SUs experience symptoms consistent with hypoglycemia over a 6-month period with 6% of the patients having hypoglycemic symptoms in a month.<sup>252,253</sup> Shorr et al. while studying the incidence and risk factors for developing serious hypoglycemia among older persons using sulfonylureas or insulin in a population-based, retrospective cohort study of 19932 Tennessee Medicaid enrollees, aged 65 years or older taking SUs or insulin identified 586 persons with a first episode of serious hypoglycemia during 33,048 person-years of insulin or sulfonylurea use thereby giving crude rates of 1.23/100 person years for serious hypoglycemia (95% confidence interval [CI], 1.08-1.38) in users of sulfonylureas and 2.76/100 person years (95% CI, 2.47-3.06) among insulin users and 3.38/100 person years in patients using both. The adjusted relative risk was 0.2 for tolbutamide, 0.6 for glipizide and tolazamide, and 1.0 for glibenclamide in comparison to chlorpropamide. The authors also reported that that recent hospitalization was the strongest predictor of hypoglycemia in the elderly population<sup>211,252</sup>. Vickova et al. reported rates of 157.1 per 10 000 person-years in nateglinide users and 203.2 per 10 000 person-years in repaglinide users.<sup>254,255</sup>

Thus, it can be seen from the literature that the incidence of hypoglycemia is widespread in T2DM patients on SU therapy and that this has the potential to be the limiting factor in the attainment of the target goals for glycemic control. Thus, experts largely advice prudent setting of glycemic targets as well as careful selection and dosing of the oral diabetic agents based on various patient and other environmental factors.

#### *4.1.4 Persistence with Sulfonylureas*

The relationship between persistence to SU therapy and health outcomes has been previously explored in a number of studies. Boccuzzi et al. noted that in patients who continuously refilled a prescription for their initial oral antidiabetic within 1.5 times the days' supply of the previous fill, the rate of discontinuation for sulfonylureas was less than that for metformin (11.3% vs 11.9%).<sup>109</sup> In contrast, Dailey et al. examined drug use patterns among patients with T2DM to understand drug use patterns among Medicaid recipients and assess their persistence to different antidiabetic regimens. After following 37,431 patients for a year, the authors found that 85.3% of the sample on monotherapy was taking a sulfonylurea among whom 15% of the patients remained persistent in comparison to the 14% who were on metformin monotherapy among whom 16% remained persistent.<sup>256</sup> Jermendy et al. compared the persistence of diabetic patients initiated on metformin or a SU to patients newly prescribed statin or clopidogrel therapy and found that the 1-year persistence of initial treatment with metformin, sulfonylureas or metformin/sulfonylureas combination was 47.7%, 45.4% and 55.8%, respectively. This though higher than statin therapy (26.3%), was still sub optimal.<sup>257</sup> Similarly, Sclar et al. in a study of Medicaid recipients in South Carolina exhibited low treatment persistence in SU users, with only 39.4% of the study population obtaining at least a 6 month supply.<sup>258</sup> Hertz and colleagues conducted a retrospective cohort study of 6090 newly treated

patients aged 18-64 years to determine adherence with pharmacotherapy for T2DM found that 9.7% of patients initiated on sulfonylureas were non-persistent at an early stage while almost 34% of the patients were non-persistent at the end of a year.<sup>259</sup> Grégoire et al. assessed persistence patterns with oral antidiabetic medications in a population-based cohort study. They found that the likelihood of continuing the with the initially prescribed oral antidiabetic medication over a 12 month period was 56% for SUs, which was about 10% less than that for metformin. In another study, Ligueros-Saylan and colleagues found that almost 44% of the patients on SUs discontinued their therapy within one year of initiation.<sup>260</sup> The risk of medication discontinuation during the follow up period was significantly higher for patients who were prescribed sulfonylureas as compared to metformin, the likelihood of (Adjusted Hazard Ratio: 1.32; 95% CI 1.29–1.34) and probability of restarting the therapy after discontinuation was less likely (Adjusted Hazard Ratio: 0.91; 95% CI 0.89–0.93).<sup>261</sup>

It is well understood from previous literature that persistence with medications is a vital factor in achieving optimal glycemic control. A large body of literature also points to the fact that treatment non persistence is a frequent issue related to oral antidiabetic medications including sulfonylureas. Cramer et al., while reviewing studies of patient compliance and persistence with cardiovascular or antidiabetic medications, suggested that even though the overall persistence rate for oral antidiabetics was comparable to other therapeutic classes of medications for various diseases, noncompliance with antidiabetic medication was still a grave issue with the results showing that the 12-month persistence of oral antidiabetics was 62% with



almost 30% of days of therapy not covered by medication and only 59% of patients having medication for more than 80% of their days on therapy in the year.<sup>107</sup> It has also been shown in various studies that conforming to the medication regimen can significantly decrease the utilization of medical resources. For example, Hepke et al. conducted a study in a non-managed care setting and concluded that higher degree of medication adherence was associated with reduced use of emergency department and inpatient visits.<sup>262</sup> Thus considering the association between medication persistence and positive health outcomes including achievement of glycemic control and reducing complications and hospitalizations as well as medical costs, it becomes necessary to explore the association between medication persistence to SUs and various patient related factors, one of them being hypoglycemic events.

#### *4.2 Rationale And Objectives Of The Study*

Data suggests that intensive glycemic control, though beneficial in minimizing several complications of diabetes may sometimes act as a precursor to incidence of hypoglycemia.<sup>95,200,263</sup> Recurrent hypoglycemia is associated with significant morbidity and often leads to negative health outcomes with respect to ideal diabetes management. Moreover, there is evidence that hypoglycemia may create a barrier to medication adherence. For example, Walz et al. evaluated the impact of symptomatic hypoglycemia on medication adherence, satisfaction with treatment, and glycemic control in patients with T2DM and reported that patients who experienced moderate or worse symptoms of hypoglycemia reported poorer adherence to medication (46% versus 67%; p-value <0.01) and were more likely to report barriers such as “bothered by medication side effects” (36% versus 14%; P-value <0.001) compared with patients with no hypoglycemia or mild symptoms of hypoglycemia.<sup>264</sup> Similarly, Lopez et al. carried out a retrospective study in adults with T2DM taking antidiabetic agents and found that 55.7% of the patients had at least one hypoglycemic event. Among patients taking antidiabetic medications, 52% reported medium to low adherence with their medications, with almost 60% of people with medium to low adherence having experienced a recent episode of hypoglycemia.<sup>265</sup> The RECAP-DM (Real-Life Effectiveness and Care Patterns of Diabetes Management) study, a multicentre study was conducted in seven countries, evaluated the association of patient-reported hypoglycemic symptoms with treatment satisfaction and barriers to adherence. The study focused on the addition of a sulfonylureas or a thiazolidinedione to ongoing

metformin therapy. Nevertheless, 38% of patients reported hypoglycemic symptoms during the previous year, patients with hypoglycemic symptoms were more likely to report barriers to adherence.<sup>181</sup>

Although various aspects of medication adherence in diabetes therapy have been investigated, studies which have focused on evaluating the impact of hypoglycemia on the adherence and persistence to SU therapy have been scarce. Medication persistence and treatment continuation could be altered in patients on SU therapy who experience hypoglycemic events due to number of reasons including fear of hypoglycemic events, impaired physical functioning as well as the impact on the quality of life, social well-being and activities of daily living. Studies report approximately 7% of patients on SU therapy experience one or more episodes of severe hypoglycemia per year, with hypoglycemic episodes potentially affecting decisions to discontinue treatment. It is essential to understand and describe differences in medication persistence in patients taking SU therapy related to hypoglycemia.<sup>213</sup> Therefore, the aim of this study was quantify the effect of hypoglycemia on persistence rates with oral SU therapy.

## *4.3 Methods*

### *4.3.1 Datasource*

For the purpose of our study, we used the Blue Cross and Blue Shield Of Rhode Island (BCBSRI) administrative claims data for the years 2009 - 2012. BCBSRI is a non-profit hospital service and medical service corporation covering more than 600,000 members. In the data extract used for our analyses, all the members had at least one International Classification of Disease-9 (ICD-9) code for diabetes (ICD-9 250.XX) between 2009 and 2012. To achieve the aims of our study, we utilized three administrative files, including eligibility files, medical claims (inpatient and outpatient) and pharmacy claims. The enrollment file included age, gender as well as the start and end dates for enrollment in the health plan. Similarly, the outpatient and inpatient files include diagnosis information (ICD-9 codes), Current Procedural Terminology (CPT) codes, admit and discharge dates as well as cost and copayment information. The medication claims dataset included prescription medications dispensed during the study period and included the National Drug Codes (NDC), drug product names, prescription quantity (number of units dispensed) and days supplied at the time of dispensing (e.g. 30 day supply of medication). Due to the comprehensive nature of the claims provided in the dataset, it can be assumed that this dataset provides a near complete picture of an individual's health care.

#### 4.3.2. Research Design And Study Population

Using the inpatient and outpatient medical claims, and prescription claims, we conducted a retrospective cohort study using a new user design (Figure 4.1).<sup>266</sup> As our focus was on patients taking SU therapy, we further identified patients in the dataset who initiated treatment with a SU. More specifically, we utilized the following inclusion and exclusion criteria:

##### Inclusion Criteria:

- At least 18 years of age. Patient age was calculated as of the date of first SU fill.
- At least 1 prescription claim for an SU Oral Antidiabetic Drug (OAD).
- Continuous enrollment in the health plan for at least 12 months after the initial SU fill date.

##### Exclusion Criteria:

- At least one claim for type 1 diabetes (ICD-9 250.X1 or 250.X3) or gestational diabetes (ICD-9-CM 648) within the baseline period.

Since we required a continuous eligibility period of 12 months following the cohort entry for each patient, we constructed eligibility episodes for each unique patient by considering the eligibility episode separate if there was a lag of 30 or more days between the end date of the previous episode and the start date of the next episode. We only considered the eligibility episode in which the first prescription was recorded. Thus, after the initial identification of the patient cohort, we created the

cohort entry date as an indicator of the first date of fill for a SU. We further divided the study period for each patient into two phases: the baseline period and the post baseline period (Figure 4.2). The duration of the baseline phase was 3 months from the date of the first SU fill. The length of the post baseline phase was 9 months from the end date of baseline arm of the study. Thus, we followed each identified patient for a total maximum duration of 12 months starting on the first date of SU fill. An overview of study design is presented in Figure 4.2. Further, we assessed the hypoglycemia exposure, demographics, other diabetic medication exposure as well as history of comorbid conditions within the baseline arm or the first 3 months of the study after the first date of fill.

#### *4.3.3 Exposure To The Medication Class Of Interest (SUs)*

As mentioned earlier, the BCBSRI data includes information on the use of prescription drugs by the patients in the health plan and can be linked to the inpatient and outpatients medical claim files using a unique identifier. Utilizing the prescription claims data, we identified the use of medications in the patient population by using a combination of NDC codes as well as generic and brand product names. NDC codes are unique, three-segment numbers, usually 10 digits in length, which act as a universal product identifier for drugs. Further, for verification purposes, we used the Redbook 2008 to link the therapeutic groups and therapeutic classes to the drug records in the dataset. Moreover, we excluded observations if patient had day of supply less than or equal to 0 as well as those patients who had

days of supply more than 180. Using the aforementioned methods, we identified all the patients who received their first prescription for SU along the duration of the study. It has been noted in literature that patients with T2DM are often treated with a variety of concomitant medication. Based on previous evidence, we established and outlined certain classes of drugs that were known to act as contributing factors to risk of hypoglycemia.

Once we identified the eligible study population, we then evaluated exposure history during the baseline period to create two exposure groups: 1) those with at least one inpatient or outpatient claim for hypoglycemia during the baseline period; and 2) those without any claims for hypoglycemia during the baseline period. Hypoglycemic exposure was defined as the first hypoglycemic event within the baseline period requiring medical attention in either the inpatient or outpatient setting. To identify these hypoglycemic events we used the algorithm suggested by Ginde and colleagues.<sup>187</sup> This algorithm identifies an hypoglycemic event if any hospital and clinic visits are indicative of hypoglycemia by using standard ICD-9 codes (ICD-9: 251.0, 251.1, 251.2, 270.3, 962.3). Further if there is absence of hypoglycemia but presence of diabetes with other specified manifestations (ICD-9 : 250.8) without other contributing diagnoses (ICD-9 : 259.8, 272.7, 681.XX, 682.XX, 686.9X, 707.1-707.9, 709.3, 730.0-730.2 or 731.8), then such incidents are also termed as a hypoglycemic event. This algorithm is well validated and demonstrated an 89% positive predictive value (PPV) (95%CI,86–92) in accurately identifying hypoglycemia visits and an exhibited an estimated 97% sensitivity and > 99 specificity.<sup>187,263</sup> It has

been well documented that severe episodes of hypoglycemia are often followed in quick succession by further hypoglycemic events. Hence, while characterizing the subsequent events of hypoglycemia following the first incident, we counted the events that occurred with a minimum gap of 7 days between them as separate event, else the entire hypoglycemic episode was considered as a single event. Using this information, we created two groups of individuals, those with at least one hypoglycemic event during the baseline period and those without. As our interest was in incident discontinuation following hypoglycemia, we excluded patients with treatment discontinuation (n= 16) before an event of hypoglycemia within the baseline period.

#### *4.3.4 Outcome of interest : SU Treatment Discontinuation*

We followed all persons in both exposure groups for SU medication discontinuation until the end of the follow-up period. We defined discontinuation as a gap of > 30 days in SU prescription availability that occurred between consecutive prescriptions. Usually, the gap period allowed in various retrospective studies varies from 30 to 90 days or 1.5x last days supply.<sup>267</sup> Based on the clinical relevance to hypoglycemia and the day's supply limits, we chose a window of 30 days to be appropriate. This period was considered as a period where the patients would not anticipate suboptimal or negative health outcomes.<sup>267,268</sup> If another refill of the SU was filled within the specified window from the end date of the preceding prescription's days of supply, the patient was considered persistent. The persistence in terms of days to



discontinuation was calculated for the entire SU drug class, allowing for switches within the same class (i.e. patients switched from one SU agent to another). We followed all patients to the first of three endpoints: 1) time to discontinuation; 2) a subsequent hypoglycemic episode; or 3) the end of the study period. An overview of outcome identification is presented in Figure 2.

#### *4.3.5 Demographics and Comorbidities*

We compared the demographic as well as clinical characteristics between the hypoglycemia exposed and the hypoglycemia non exposed cohorts during the initial baseline period of the study. This process was carried out to characterize the potential confounding effects of certain patient related factors of interest like age and gender on the the risk of discontinuing the SU therapy. Since age was recorded as the age at the end of the enrollement period, we re-calculated the age at the date of the first fill of SU for all the patients in the study.

We used the inpatient as well as outpatient claims records for characterising the presence of comorbidities in patients. We identified the ICD-9 codes in these files to ascertain the presence of certain macro- and microvascular complications of diabetes as well as other conditions like Addison's disease and hypothyroidism which are associated with diabetes by employing methodologies that have been applied in other studies. We calculated a overall point estimate of comorbidity by application of the Deyo adaptation of the Charlson's Comorbidity Index.<sup>263,269</sup> As a part of this comorbidity index, scores from a minimum of 1 to a maximum of 6 were assigned

with different weights, to each of the 19 selected medical conditions based on their adjusted relative risks and were then summed into a composite score for each individual patient. In addition to the overall comorbidity score, we also evaluated the individual comorbidities that might have an association with hypoglycemia. This was done by using the Quan H. 's enhanced ICD-9 codes of the Deyo's adaptation of the Elixhauser Comorbidity Index. The performance and validity of the Charlson and Elixhauser comorbidity indices in predicting health outcomes has been previously evaluated in a variety of population studies where they have been consistent as prognostic measures of outcomes.<sup>270</sup> The presence of each comorbidity were recorded as a categorical dichotomous variable.

Similar to the SU identification, we also characterized the use of other medications in the baseline arm of the study by using a combination of NDC codes, product names as well the therapeutic classes and groups. The specific classes of drugs that we were interested in evaluating were angiotensin converting enzyme (ACE) inhibitors, angiotensin 2 receptor blockers (ARB), allopurinol, benzodiazepines, beta-blockers, fibrates, fluoroquinolones, non-steroidal anti-inflammatory drugs (NSAIDs), trimethoprim and warfarin.<sup>190,208</sup> The presence of each drug class were recorded as a categorical dichotomous variable. We also created a continuous variable to identify the total number of unique medications that were used by each patient since it is a known factor affecting medication persistence.

#### *4.3.6 Statistical Analyses*

In our initial phase of analyses, we compared demographic and clinical characteristics between the two exposure groups to determine group comparability. Differences between exposure and non exposure group were assessed using the Pearson's chi-square test or Fisher exact test in case of the categorical variables and Student t-test or Mann Whitney U test for the continuous variables. We also conducted a descriptive analysis of the outcome variable and computed the total time to discontinuation SU therapy by hypoglycemia exposure status thereby reporting the mean time to discontinuation in both groups.

Since there would be a certain lag between the first prescription of SU to the first instance of hypoglycemia in the hypoglycemia exposed cohort, a certain degree of immortal time bias was introduced due to the fact that hypoglycemia exposed cohort would not experience the discontinuation outcome prior to exposure (Appendix 4.12). To account for this phenomena, we adjusted for during immortal time in the exposed group during our statistical analysis.<sup>271-273</sup> The schematic representation of immortal time bias is shown in Figure 3. We adjusted for this immortal time bias in our statistical analyses by moving the start of follow-up or exposed time to the end of the immortal period while accounting for the time between cohort entry and exposure date as unexposed time.

At this stage we had outlined the individual variables which were identified as potential confounders during bivariate analyses based on either their clinical relevance or their independent bivariate association with hypoglycemic exposure. To identify the impact of the hypoglycemia exposure on the persistence of SU therapy in terms of time to discontinuation, we developed a time varying Cox proportional-hazards model that was based upon the estimates of the descriptive bivariate analyses in the first phase of analytical process. The anti-log transformation of coefficients derived from this model were utilized to calculate Hazard Ratios (HR) comparing the relative hazard of discontinuing medication in the hypoglycemia exposure group compared to the hypoglycemia non-exposure group while adjusting for the immortal time bias in the hypoglycemia exposed group. In the general form of the time-varying Cox-Proportional Hazards model is<sup>274</sup>

$$h(t|X) = h(t) \exp(X_1\beta_1 + \dots + X_p \beta_p).$$

The dependent variable in our model was the time from the first date of SU prescription to the date of discontinuation of the therapy which was the date on which the days of supply of the last prescription ended. The independent variable of interest was hypoglycemia exposure, and operationalized as time varying (1=hypoglycemia exposure, 0=Hypoglycemia Unexposure). We used the method suggested by Suissa et al. in order to define the time varying nature of the hypoglycemia exposure. The status of a patient was considered unexposed from the

date of the cohort entry until the date of the hypoglycemic event and thereafter exposed until the end of follow-up.<sup>271,273</sup>

Other confounding variables that were found significantly associated with hypoglycemic were eligible for entry into the model if they had atleast a 10% difference between the hypoglycemia exposed and hypoglycemia unexposed groups during bivariate anlyses. We then fitted sequential models in a nested manner by means of a manual non-computer generated forward stepwise approach. We assessed the B-coefficient for the hypoglycemia exposure group from the model at each step when the confounding factor was added. If there was a 10% change in the B-coefficient for hypoglycemia exposure in the model in comparison to the model without the added confounding factor then it warranted the inclusion of the confounding factor and it was retained in the model. These stepwise iterations were continued until the most parsimonious model was fitted according to the proposed criteria.

Once the preliminary model was fitted, we assessed the mulitcollinearity in the retained variables using variance inflation factor (VIF) and the Condition Index (CX). If the value of VIF exceeded 5, we considered that there was a high degree of multicollinearity between two covariates and warranted one to be removed from the model based on the p-value and clinical importance. We further evaluated two-way interactions between biologically and clinically plausible variables that were retained in the preliminary model. The interaction terms were sequentially added and the

model with the interaction term was compared to the model without the interaction term by means of likelihood ratio tests. Lastly, we also examined the model for any violations of the proportional hazards assumption by visual inspection of the survival curves.<sup>152,153</sup> We used Akaike Information Criterion (AIC) at all steps of building the final model, since AIC is asymptotically equivalent to cross-validation and the bootstrap, two most popular validation methods. Also a likelihood test was conducted to evaluate the final model. We estimated and reported crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) from the crude and final models.

We also performed a power and sample size calculation based on the rate of medication discontinuation. We considered two-sided alpha level constant at 0.05 and based on our analyses, set the rate of medication discontinuation at 0.60. We considered a that a 5% change in the rate of medication discontinuations between groups is a clinically meaningful difference thereby setting the regression coefficient at 0.05. Since there are no sample size estimations available that take into account for the time-varying nature of the exposure for a Cox proportional-hazards model, we estimated the power of our study based on time fixed methods.

All statistical tests were conducted with a two-tailed alpha level of 0.05, and all statistical analyses in this study were performed using SAS software (SAS Institute Inc., Cary, NC, Version 9.3). Sample size calculations were conducted using using PASS

software (2014 version; NCSS, Kaysville, UT). This study was reviewed and approved as exempt by the University of Rhode Island's Institutional Review Board.

#### 4.4 Results

##### Cohort Identification

The study sample was comprised of 36,954 individuals. Figures 4.3 and 4.4 give an detailed explanation of the patient selection process. During the study period, 9,686 patients were initiated on SU therapy. Among SU users, 8,229 (85.0%) patients were given a 30 day supply of medication while 1,153 patients were given a 90 day supply (11.9%). Out of the study sample taking SUs, a total of 5,390 (55.7%) patients recorded only one episode of SU drug use which might indicate complete persistence or discontinuation after a single episode of SU use. In contrast about 4.9% of the patients on SU therapy recorded more than 5 drug use episodes over the course of the study. In this eligible sample of patients, 5,442 (56.2%) patients did not persist to their medication and discontinued it at some point during the study follow up period. The incidence of discontinuation is presented in Table 4.1. Overall, 2,016 patients (34.0%) discontinued their medication. Within the unexposed cohort, 1,996 patients (34.0%) discontinued their SU therapy at some point during the post baseline period, while 20 patients (36.4%) of the exposed cohort discontinued their medication ( $\chi^2=0.14$ ,; p-value: 0.70).

According to inpatient records in the dataset, a total of 1,295 patients had an inpatient hypoglycemic events requiring medical attention occurred and 2,368 patients had an outpatient visits for hypoglycemia occurred. Within the baseline period, 139 had a hypoglycemic episode for an overall risk of 0.37% over 3 months.



Table 4.2 presents the basic demographic characteristics of the final study sample. Age was comparable in the two exposure groups with a mean age (SD) at the index date of first SU prescription of 64.9 years [11.21] and 64.5 [12.48] in the hypoglycemia group and unexposed group, respectively. Gender distribution was similar across the two cohorts with 56.4% of the hypoglycemia-exposed cohort (31 patients) and 57.2% (3,363 patients) of the patients in the exposed and unexposed cohorts respectively being female ( $X^2=0.01$ ; p-value: 0.90). Nine patients (16.4%) in the exposed cohort were using insulin in the baseline period in contrast to the 533 patients in the unexposed cohort (9.1%;  $X^2=3.49$ ; p-value: 0.06).

The prevalence of the comorbidities stratified by hypoglycemic exposure is summarized in Table 4.3. The average Charlson's comorbidity scores (SD) were observed to be higher in the hypoglycemic cohort (3.78 [2.82]) as compared to the hypoglycemia unexposed cohort (2.45 [2.43]; p value 0.001). Prevalence of all these conditions was observed to be notably higher in the hypoglycemia exposed group. Chronic pulmonary disease was diagnosed in 14.6% of patients with hypoglycemia in contrast to the 4.5% in patients who did not experience hypoglycemia ( $X^2=12.68$ ; p value=0.0004). Similarly, congestive heart failure was seen 9.1% of the hypoglycemia exposed cohort and 3.6% of the hypoglycemia unexposed cohort ( $X^2=4.75$ ; p value: 0.02). Moreover, in the hypoglycemia group, 80% had a diagnosis of uncomplicated diabetes and 72.7% were diagnosed with complicated diabetes ( $X^2: 3.51$ , p value: 0.06). As opposed to the exposed cohort, the unexposed cohort had a lower frequency of both diabetes with and without complications (896, 15.24% and 3545,

60.30% respectively) ( $X^2$ : 171.41, p value: <0.001). Other factors are presented in Table 3 and were consistently higher in the hypoglycemia group versus the non-exposed group.

The overview of the microvascular and macrovascular complications associated with diabetes is displayed in Table 4.4. Congestive heart failure was much more prevalent in the diabetic patients who had an event of hypoglycemia with 9.1% being diagnosed with this disorder compared to the 2.7% in the unexposed cohort ( $X^2=8.55$  p value: 0.003). Similarly, the patients in the exposed cohort had a higher prevalence of coronary artery disease (16.1% vs 10.3%;  $X^2=2.33$  p-value=0.12). Patients with hypoglycemia events had a higher prevalence of diabetic retinopathy (10.9% vs 5.0%,  $X^2= 29.22$ ; p value=0.04) ulcer (7.3% vs 1.8%;  $X^2= 76.89$ ; p value=0.002) and thyroid disease (7.3% vs 2.8%;  $X^2= 90.17$ ; p value=0.02) in contrast to those who did not experience any hypoglycemia events.

Table 4.5 outlines a brief overview of the other medications that were concomitantly used during the baseline period. Of those who exposed an event of hypoglycemia, the average number of unique medications used was (8.63 +/- 3.84) which was higher than drug use by the patients who did not experience an event of hypoglycemia (7.16 +/- 3.67) during the baseline period. Notably, the use of benzodiazepines were higher in the hypoglycemia group (14.6%) than in the unexposed group (9.0%;  $X^2=2.03$ ; p value=0.1535). With respect to other medications that were considered for analyses, the unexposed group was found to

be using these medications to a higher degree. For example, with in case of warfarin, 5.9% in the unexposed group and 3.6% in the hypoglycemia group were using this medication ( $X^2=0.51$ ; p-value=0.47).

Table 4.6 summarizes the use of other oral antidiabetic medications by the patients during the baseline period. 37 patients (67.27%) within the exposed cohort were using the biguanide class of oral antidiabetic medications simultaneously during the baseline period as compared to 3639 patients (61.90%) in the hypoglycemia unexposed group ( $X^2= 0.66$ , p value= 0.41). Similarly, the frequency of use of TZDs was higher in the hypoglycemia exposed group with 11 patients (20%) using these medications as opposed to the 950 patients (11.11%) in the hypoglycemia unexposed group ( $X^2=0.59$ , p value=0.44). The use of alpha glucosidase inhibitors and meglitinides was also higher in the hypoglycemia exposed group as compared to the hypoglycemia unexposed group (1.82% vs 0.27%, 1.82% vs 0.19% respectively)(  $X^2 4.55$ , p value=0.03 and  $X^2= 7,18$ , p value= 0.0074 respectively). The frequency of using DPP 4 inhibitors was identical in both cohorts with 5 and 505 patients (9.09% and 8.59% respectively) in the exposed and unexposed cohort using this medication (  $X^2=0.01$ , p value= 0.89).

Estimates for the accrued person time by both the study cohorts as well as the crude and adjusted hazards ratios are presented in Table 4.7. Patients in the hypoglycemia exposed cohort accrued 12,908 person days of follow up (Mean=234.69) during the course of the study period while patients in the hypoglycemia unexposed cohort

accrued 1,789,222 days of follow up (Mean=304.31). The misclassified immortal time contributed by the patients from the exposed cohort that had to be accounted for as unexposed time was estimated to be 2,250 person days of follow-up.

The results of the Cox Proportional Hazards model are presented in Table 4.7. Age and gender were included in the model irrespective of their significance during bivariate analyses because of their biological importance. The crude HR for discontinuation of SU medication was 1.47 (95% CI: 0.94 – 2.28). After adjusting for effects of all the covariates under consideration, the HR for discontinuation of SU medication was 1.32 (95% CI: 0.82 – 2.11). Thus, in both unadjusted analyses and analyses that adjusted for relevant confounding variables, it could be seen that there was a 47% and 32% elevation in the rate of medication discontinuation. Based on our sample size, our study had approximately 82% power to detect a hazard ratio of 1.05.

#### *4.5 Discussion*

Our current study sought to determine the impact of severe hypoglycemic episodes requiring medical intervention on the persistence of the oral SU therapy. According to our findings, though the patients who experience an event of hypoglycemia in the baseline period are approximately 30% more likely to discontinue their medication, this association was not statistically significant. To our knowledge, there have been no previous studies that have specifically evaluated the impact of hypoglycemia on the time to discontinuation of SU medications following hypoglycemic exposure using a new user design.

We utilized an incident user design while conducting this study. This design was preferred since it enabled us to capture all the hypoglycemia events that occurred soon after initiation of the SU therapy. Ray et al. while reviewing the new user designs, clearly state that even with medications, rate of outcomes, both beneficial as well as adverse, varies with time since the initiation of therapy with the probability of the outcome being the maximum immediately after the start of the medication regimen.<sup>266</sup> Hence using this design ensured that we accounted for even those patients that were more susceptible to hypoglycemic effects of this medication regimen as opposed to other designs that might have been incapable of selecting these patients.<sup>275</sup> For example, in a study to assess the risk of venous thromboembolism (VTE), associated with newer oral contraceptives, Suissa et al. did not distinguish between new users, repeaters and switchers and thereby found an

excess risk of VTE associated with the use of third generation oral contraceptives. The authors recognized the bias in this study and attributed it to the non-differentiation between the three different user groups.<sup>276</sup> In addition, this type of study design also helps alleviate the need to methodically adjust for covariates that lie in the casual pathway.<sup>266,277</sup>

Though the risk of hypoglycemia is widely recognized in the treatment of Type 1 Diabetes, there is increasing recognition of this issue in T2DM. Seaquist and Associates reported that many trials like the ACCORD and ADVANCE have suggested that T2DM patients might be at a greater risk of adverse events associated with instances of hypoglycemia, including mortality.<sup>278</sup> Mitchell et al. in an online survey of 1,329 T2D patients in United Kingdom (UK), found that 23% of patients who used oral glucose lowering medications in absence of insulin experienced hypoglycemic events.<sup>279</sup> Leckie and colleagues conducted a prospective 12-month survey of 243 employed people to examine the frequency and consequences of hypoglycemia. They found the rate of severe hypoglycemic events to be 0.14 episodes per person per year and concluded that this rate was lower than the rates of 1.1–1.7 episodes per patient per year that have been reported in previous Northern European studies.<sup>224</sup>

Our decision to choose the SUs as the drug class of interest was based on the fact that it has been traditionally established in various prospective and retrospective studies that among all the oral antidiabetic medications, SUs are associated with a

higher propensity to cause hypoglycemic episodes. In our study we found that among the 26.2% of patients who were initiated on an oral SU regimen, 3.9% of the patients had at least one event of hypoglycemia. In our final study sample, 0.9% of patients experienced a hypoglycemic event. Our study indicated a clear evidence of recurrence of hypoglycemic events, with patients experiencing multiple hypoglycemic incidents requiring medical attention.

Other studies have reported varying rates for the incidence of hypoglycemic episodes with SUs. For example, In the UKPDS, the mean rate of severe hypoglycemic events was 18% at the end of 10 years of follow-up. In a study conducted by the UK Hypoglycemia Study Group, 39% of the patients on SU medication reported severe hypoglycemic events.<sup>213</sup> Miller et al. evaluated the prevalence and risk factors for hypoglycemic in 1055 patients with T2DM and found that only 5 patients (0.5%) suffered from severe hypoglycemia and that all these patients were insulin users.<sup>195</sup> Van Staa et al., using the UK General Practice Research Database, reported that 1.8% users of SUs suffered from an incident of hypoglycemia with patients using glibenclamide being at the highest risk.<sup>249</sup> Jennings et al. investigated the prevalence of hypoglycemia in patients treated with oral hypoglycemic agents and reported that 20% of patients treated with sulfonylureas had symptoms of hypoglycemia during the previous 6 months.<sup>253</sup> Bodmer et al. in a case control study to compare the risk of lactic acidosis and hypoglycemia among patients with type 2 diabetes using oral antidiabetic drugs found the rate of mild/moderate or severe hypoglycemia was 60 per 100,000 person years for sulfonylureas.<sup>197</sup> Thus, in the context of the pertinent

issue, the rates that were found in our study are clinical significant findings considering the number of patients that receive SU, either alone or as part of combination therapy every year even though previous literature has documented a relatively low risk of severe hypoglycemia in patients with T2DM. In addition, our results could not be satisfactorily compared to these previous studies owing to the differences in make-up of the study population, study designs, and definitions of the hypoglycemic events.

We observed the persistence rates to oral SU medications from the cohort entry date to the end of follow up period, which was a time span of 1 year. We observed that the rate of medication discontinuation in our study was about 34.0%, with almost one third of the patients in the exposed cohort discontinuing their medication within the 9 month follow-up period. The principal finding of our study indicates that the after adjusting for all relevant covariates, patients who are exposed to hypoglycemic episodes are approximately 30% more likely to discontinue their medication regimen than those who do not experience hypoglycemia, although this finding does not attain statistical significance.

Cramer et al., in their review of literature, reported that the overall average persistence rate for oral antihyperglycemic agents was 62.3% with the rate dropping to 51.1% for studies conducted in the US.<sup>107</sup> It has to be noted however that the review failed to take into consideration the potential misclassification of studies as well as the class differences in the medications under consideration. In another



review investigating adherence to diabetic medications, Cramer et al. noted that the rate of people continuing with their medications varied from 16% to 80% during a treatment time of 6–24 months while the time to discontinuation of medications was 83–300 days.<sup>108</sup> Similarly, Grégoire et al. found the persistence rates in newly initiated SU therapy to be 56% and concluded that in comparison to metformin, SUs displayed a poorer persistence profile. However, it was unclear in this study whether the discontinuation was due to lack of clinical efficacy, adverse events, or any other causes.<sup>261</sup> Similarly, Sclar et al., Skaer et al, and Bocuzzi et al. demonstrated rates of 44%, 58% and 60% respectively for SU therapy during the first year.<sup>109,258,280</sup> Rathmann and colleagues, in a study to investigate therapy persistence and other factors in DPP-4 inhibitors and SUs, found the rate of discontinuation with the SUs to be 49%, which was 10% higher than that for DPP-4 inhibitors.<sup>281</sup> Moreover, it should be seen that this study did not take into account the validity of the type of diabetes the patients were suffering from as well as the prescribed daily dosages of the medications<sup>281</sup>. In another European study, Jeremendy et al. found that the rate of SU persistence was only about 49%.<sup>257</sup>

Our estimates should be viewed in light of some important differences with other studies. A variety of definitions of persistence have been used in various studies. Similarly, it is vital to understand that simply refilling the drug doesn't necessarily indicate persistence and that there are very few suitable means to evaluate the actual medication taking behavior of people. Further, in studies of medication compliance, it can be seen that the follow up times as well as the defined gap in

medication refill in terms number of days can vary largely. In contrast to other studies, we regarded a switch to other oral medications as a discontinuation of SU therapy, potentially accounting for variation in rates between our study and previously published studies.

While our study was intended to principally analyze the impact of hypoglycemia on medication discontinuation, we found some other factors that were significantly associated with discontinuation of medication namely age, number of concomitant medications as well as use of insulin in the baseline period. It could be seen that the increase in age was significantly associated with better persistence to medications. This is in agreement with previous studies that have investigated the relationship of age and persistence. For instance, Guénette et al. reported that patients aged 54 years or above were more likely to be persistent to their antidiabetic medications as compared with those aged from 18 to 53 with people over the age of 75 being more than 44% more likely to persist with their medications.<sup>110</sup> Similarly, Hertz et al. demonstrated that younger age was significantly associated with discontinuation of medication with patients between ages 17 – 24 being much more likely to have discontinued therapy (HR=2.44, 95% CI 1.89 – 3.15) as compared to patients between ages 50 and 64.<sup>259</sup> One possible explanation for this finding would be greater realization of the dependency of their health on therapy as compared to people who are younger. Our finding that treatment with insulin was associated with higher likelihood of medication discontinuation is supported by previous studies. Catalan et al. reported that elderly patients with previous insulin use were 1.59 times less likely

to persist with acarbose drug regimen as compared to those who had not received insulin.<sup>282</sup> Moreover, addition of insulin to SU might exacerbate the risk of having a hypoglycemic event thereby increasing the risk of discontinuation. In context of the progression of diabetes, poly-pharmacy to meet treatment goals is unavoidable. Hence, an interesting finding in our study was an increase in likelihood of continuing with therapy when the number of concomitant medications increased. There have been contrasting results with respect to polypharmacy and hence treatment complexity potentially being a cause of decreased therapy persistence with medications. For example, Dailey et al., Donnan et al., and Venturini et al. reported decreased compliance with increase in the number of medications.<sup>256,283,284</sup> On the other hand, Guénette et al. and Hertz et al. reported an increase in the persistence rate with higher number of concomitant medications.<sup>110,259</sup> Grant et al. found no association between multiple medications and sub optimal treatment adherence but suggested rather that side effects of certain drugs caused the non-adherent behavior.<sup>285</sup>

There is a plethora of literature that provides evidence that complex multifactorial relationship between achievement of glycemic objectives, medication compliance, and adverse events like hypoglycemia that might in turn affect them. There might be a range of clinical and behavioral aspects like adverse events, severity of illness and frequency of dosing that might be responsible for a person to adhere to the medication regimen. Moreover, with the oral antidiabetic medications, hypoglycemia, and fear of hypoglycemia are known limiting factors affecting the

rates of medication compliance. Medication tolerability issues like hypoglycemia might in turn affect an individual's perception to perform certain self-care behaviors that are essential in the management of diabetes, adhering to medications being one of them<sup>265</sup>. Certain studies have demonstrated that the additional burden placed on the patients as a consequence of the physical and psychological distress that is associated with incidence of hypoglycemia and its management might prompt them to make decisions in order to balance the unpleasant effects with achievement of glycemic goals.<sup>190</sup> In many cases it has been observed that blood glucose levels are eventually compromised in this process.<sup>286</sup> Shui et al. in a cross sectional study to investigate the fear of hypoglycaemia among 120 insulin-treated patients noted that 15% of respondents reported high fear with 19.2% of the patients compromised on their blood glucose levels.<sup>287,288</sup> Leiter and colleagues conducted a study to assess the influence of hypoglycemia and fear of future hypoglycemic episodes on patients with type 1 or insulin-treated type 2 diabetes. The authors found that among the 133 insulin-treated type 2 diabetes patients, 29.9% and 84.2% patients reported an increased fear of future hypoglycemia following a mild and severe episode of hypoglycemia respectively. The authors also suggested that this subsequently changed the patient's willingness to continue with therapy. in a Swedish study of 309 patients above the age of 35, Lundkvist et al. found that in patients who had incidents of hypoglycemia there was lower control of diabetes, worse general health and that these patients were more anxious about future hypoglycemic events than those without hypoglycemia. The authors concluded such patients exhibited a

greater degree of avoidance behavior<sup>289</sup>. Severity of the hypoglycemic episode often leads to reduced satisfaction to diabetes medication regimen, which in turn might result in a greater degree of medication discontinuation.<sup>290</sup> Although not all the aspects of the relationship between fear of hypoglycemia and compliance with the medication regimen are entirely clear, it is plausible that it acts as a major barrier to patient's medication taking behavior and thus the management of diabetes.

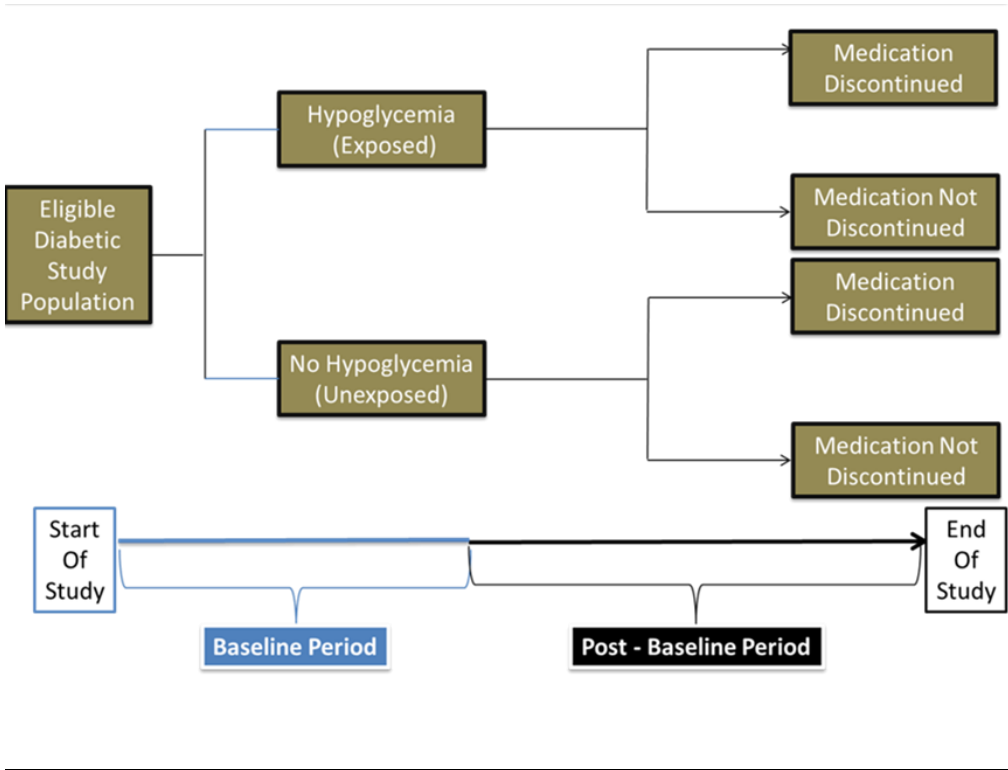
.However, since this was a retrospective cohort study using a medical claims database, some inherent limitations need to be taken into consideration. With respect to the diagnosis of hypoglycemia, it vital to understand that many of the hypoglycemia episodes resolve by themselves or get treated without a visit to any medical facility. Hence, our estimates of hypoglycemia might represent only a fraction of the true extent of this adverse event associated with diabetes therapy. Secondly, due to the nature of the datasource, examination of the clinical measures of glycemic control and disease severity were not possible and hence the impact of these measures on the likelihood of medication discontinuation could not be ascertained. Moreover, since the patients might have been on SU medications while in other insurance plans, using the incident user design does not necessarily guarantee that all the patients in the final sample are newly prescribed SU therapy. Our analysis was primarily based on the data from pharmacy drug dispensing. Hence, even though we considered failure of the patients to refill their medications as being a marker of discontinuation of therapy, in reality, there are no plausible methods to understand if this reflected the true use of medications, which might be

overestimated in case of patients who filled their prescriptions but did not take their medications. Also, extending our selection of a 3 month period as a baseline period, might have added to the capability to examine a higher number of hypoglycemia events. However, it has been seen in previous studies of chronic disease medication persistence that majority of events occur within the initial period of medication initiation. In addition to this consideration, the nature of hypoglycemia episodes in patients as well as the issue of repeated hypoglycemia events was instrumental in choosing a baseline period of 3 months.

#### *4.6 Conclusions*

Hypoglycemia is a known barrier to optimal use of oral antidiabetic medications, especially SUs. Even though we found no statistical association between the incidence of hypoglycemia and subsequent persistence to SUs, it is important to take into account the implications of hypoglycemic episodes on medication adherence. Optimal diabetes management requires timely examination of blood glucose levels and reduction in the risk of side effects like hypoglycemia when on therapy. This might be beneficial in the long-term well-being as well as the improvement in the Quality of Life (QOL) of patients. Further research must be directed towards exploring the association between hypoglycemia and other risk factors that might have an impact on medication adherence and persistence. This might provide invaluable insights into selection of an appropriate medication regimen that would provide effective glycemetic control and reduction in the risk of sub optimal health outcomes.

**Figure 4.1 Overview of Cohort Study Design: Exposure To Severe Hypoglycemia With An Outcome Of Medication Discontinuation**





**Figure 4.2: Detailed Overview Of Study Timeline**

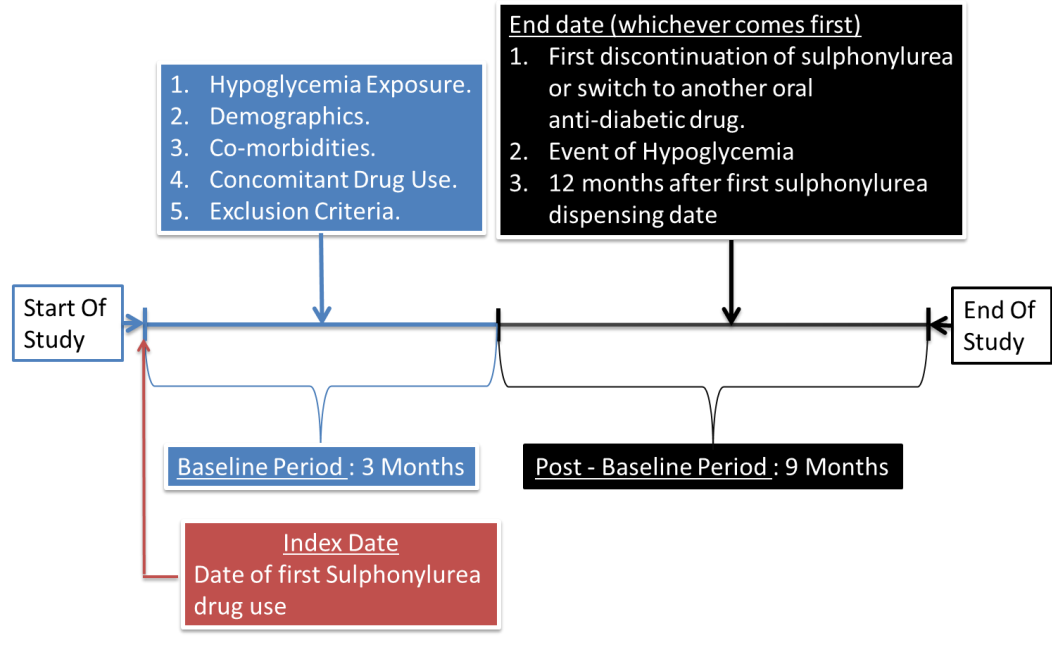
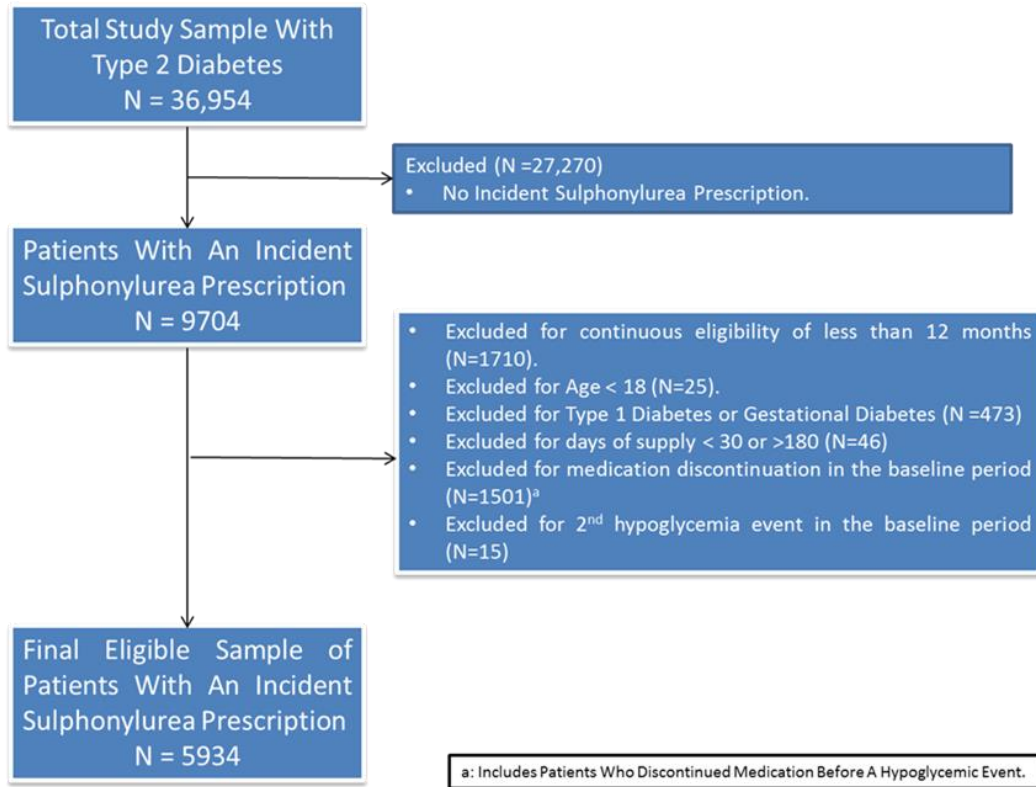
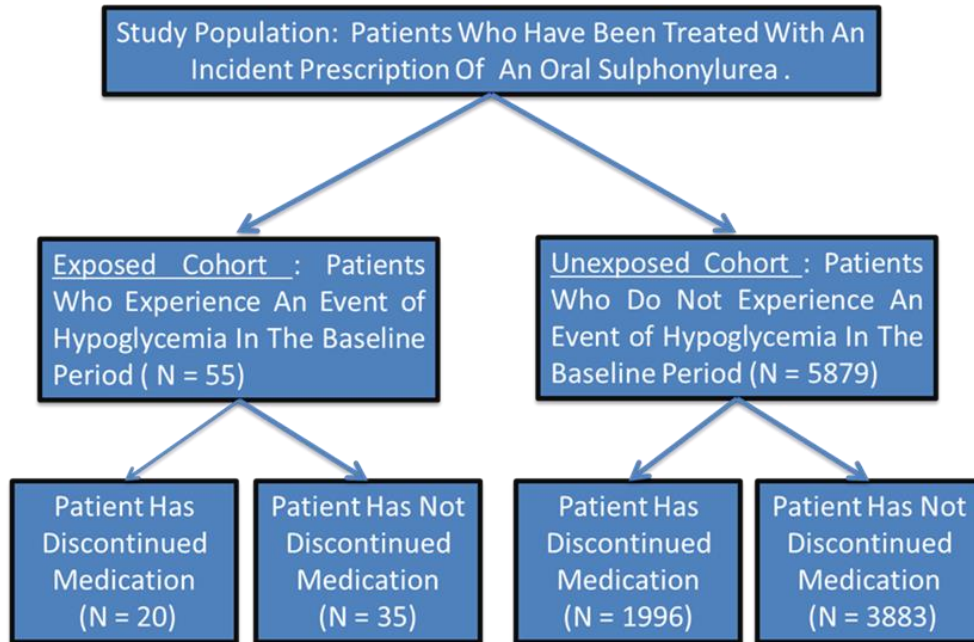


Figure 4.3: Detailed Cohort Selection of BCBSRI Enrollees



**Figure 4.4: Characterization Of The Association Between A Hypoglycemia Event  
And Medication Discontinuation**



**Table 4.1: Frequency Of Patients Who Were Persistent/Non-Persistent with Sulfonylurea Therapy Stratified By Exposure To Hypoglycemia**

<b>Hypoglycemia Outcome</b>	<b>Non Discontinued</b>	<b>Discontinued<sup>a</sup></b>	<b>Total (%)</b>
No Hypoglycemia	3,883	1,996	5,879 (99.08)
Hypoglycemia	35	20	55 (0.92)
<b>TOTAL</b>	<b>3,918</b>	<b>2,016</b>	<b>5,934</b>
a: Discontinuation: Defined as a gap of > 30 days between the end of day's pf supply of the preceding prescription and refill of the next prescription.			

**Table 4.2: Demographics Stratified by Exposure to Hypoglycemia**

Demographic Characteristics	Hypoglycemia (N = 55)	No Hypoglycemia (N = 5879)	P Value
	<u>Mean +/- STD.DEV</u>		
Age (Years) <sup>a</sup>	64.87 +/- 11.21	64.46 +/- 12.48	<0.001*
Gender <sup>b</sup>	N (%)		
Male	31 (56.36)	3363 (57.20%)	0.900
Female	24 (43.64)	2516 (42.80%)	
a: Mean + Std. Dev & the T Test were used to compare continuous variables. *: Significance at p value 0.05 as derived from T Test. b: n (%) & Cochran-Mantel-Haenszel statistic was used to compare categorical variables. +:Significance at p value 0.05 as derived from Fischer's Exact Test.			

**Table 4.3: Prevalence of Comorbidities Stratified by Exposure to Hypoglycemia**

Comorbidity	Hypoglycemia (n=55)	No Hypoglycemia (n=5879)	P-Value
Charlson's Comorbidity Index			
Charlson's Comorbidity Score <sup>a</sup>	3.78 +/- 2.82	2.45 +/- 2.43	<0.001 <sup>^</sup>
Elixhauser Comorbidity Index <sup>b</sup>			
AIDS/HIV	0 (0.00)	4 (0.07)	0.8466
Alcohol Abuse	0 (0.00)	12 (0.20)	0.7373
Blood Loss Anemia	0 (0.00)	21 (0.36)	0.6570
Cardiac Arrhythmias	1 (1.82)	364 (6.19)	0.1791 <sup>+</sup>
Chronic Pulmonary Disease	8 (14.55)	263 (4.47)	0.0004 <sup>+</sup>
Coagulopathy	1 (1.82)	18 (0.31)	0.0482 <sup>+</sup>
Congestive Heart Failure	5 (9.09)	210 (3.57)	0.0292 <sup>+</sup>
Deficiency Anemia	2 (3.64)	95 (1.62)	0.2395 <sup>+</sup>
Depression	3 (5.45)	235 (4.00)	0.5835
Diabetes Complicated	44 (80.00)	896 (15.24)	<0.001*
Diabetes Uncomplicated	40 (72.73)	3,545 (60.30)	0.0607*
Drug Abuse	0 (0.00)	11 (0.19)	0.7481
Fluid And Electrolyte Disorders	1 (1.82)	58 (0.99)	0.5361
Hypertension, Complicated	1 (1.82)	60 (1.02)	0.5594
Hypertension, Uncomplicated	9 (16.36)	1,248 (21.23)	0.3795
Hypothyroidism	4 (7.27)	155 (2.64)	0.0341 <sup>+</sup>
Liver Disease	2 (3.64)	71 (1.21)	0.1039 <sup>+</sup>
Lymphoma	0 (0.00)	24 (0.41)	0.6349
Solid tumor without metastasis	3 (5.45)	276 (4.69)	0.7910
Metastatic Cancer	0 (0.00)	10 (0.17)	0.7595
Obesity	0 (0.00)	30 (0.51)	0.5953
Other Neurological Disorders	1 (1.82)	40 (0.68)	0.3106
Paralysis	0 (0.00)	6 (0.10)	0.8126
Peptic Ulcer Disease Excluding Bleeding	0 (0.00)	2 (0.03)	0.8912
Peripheral Vascular Disorders	6 (10.91)	247 (4.20)	0.0143 <sup>+</sup>
Psychoses	0 (0.00)	24 (0.41)	0.6349
Pulmonary Circulation Disorders	1 (1.82)	29 (0.49)	0.1679 <sup>+</sup>
Renal Failure	5 (9.09)	110 (1.87)	0.0001 <sup>+</sup>
Rheumatoid Arthritis/ Collagen Vascular Diseases	1 (1.82)	77 (1.31)	0.7418
Valvular Disease	0 (0.00)	104 (1.77)	0.3197
Weight Loss	0 (0.00)	8 (0.14)	0.7843

a: Mean + (Std. Dev) & the T test was used to compare overall Charlson's Index.  
<sup>^</sup>: Significance at p value 0.05 as derived from T Test.  
b: n (%) & the Cochran-Mantel-Haenszel statistic / Fischer's Exact Test were used to compare categorical variables.  
\*: Significance at p value 0.05 as derived from Chi-square.  
+: Significance at p value 0.05 as derived from Fischer's Exact Test due to smaller sample sizes.

**Table 4.4: Prevalence of Micro and Macrovascular Diabetes Complications, Other Contributing Diseases Stratified by Exposure to Hypoglycemia**

Diabetes Complications	Hypoglycemia (n=55)	No Hypoglycemia (n=5879)	P-Value
Macrovascular <sup>a</sup>			
Arrhythmia	1 (1.82)	259 (4.41)	0.3508
Congestive Heart Failure	5 (9.09)	159 (2.70)	0.0034 <sup>+</sup>
Coronary Artery Disease	9 (16.13)	603 (10.26)	0.1383 <sup>+</sup>
Peripheral Vascular Disease	7 (12.73)	725 (12.33)	0.9293
Stroke	0 (0.00)	27 (0.46)	0.6144
Microvascular <sup>a</sup>			
Acute Renal Failure	1 (1.82)	39 (0.66)	0.2975
Amputation	0 (0.00)	2 (0.03)	0.8912
Chronic Renal Pathophysiology	1 (1.82)	33 (0.56)	0.2190
Dialysis	0 (0.00)	9 (0.15)	0.7755
End Stage Renal Disease	0 (0.00)	0 (0.00)	NA <sup>^</sup>
Diabetic Nephropathy	0 (0.00)	41 (0.70)	0.5343
Diabetic Retinopathy	6 (10.91)	293 (4.98)	0.0455 <sup>+</sup>
Ulcer	4 (7.27)	104 (1.77)	0.0024 <sup>+</sup>
Other Contributing Diseases <sup>a</sup>			
Addison's Disease	0 (0.00)	2 (0.03)	0.8912
Liver Disease	1 (1.82)	52 (0.88)	0.4638
Thyroid Disease	4 (7.27)	146 (2.78)	0.0243 <sup>+</sup>

a: n (%) & the Fischer's Exact Test were used to compare categorical variables due to smaller sample sizes.  
<sup>+</sup>: Significance at p value 0.05 as derived from Fischer's Exact Test.  
<sup>^</sup>: No p value calculated due to 0 sample size.

**Table 4.5: Concomitant Usage of Non-Diabetic Medications Stratified by Exposure to Hypoglycemia**

Medications	Hypoglycemia (N = 55)	No Hypoglycemia (N = 5879)	P-Value
Overall Medication Use <sup>a</sup>			
Number Of Medications	8.63 +/- 3.84	7.16 +/- 3.37	<0.001*
Use Of Other Non-Diabetic Medication Classes <sup>b</sup>			
ACE Inhibitors	25 (45.45)	2958 (50.31)	0.4730
Allopurinol	3 (5.45)	222 (3.78)	0.5165
Angiotensin II Receptor Blockers (ARBs)	1 (1.82)	174 (2.96)	0.6184
Benzodiazepines	8 (14.55)	529 (9.00)	0.1535 <sup>+</sup>
Beta-Adrenergic Blocking Agents	22 (40.00)	2149 (36.40)	0.5809
Fibrates	9 (16.36)	608 (10.34)	0.1453 <sup>+</sup>
Fluoroquinolones	6 (10.91)	320 (5.44)	0.0766 <sup>+</sup>
Nonsteroidal Anti-Inflammatory Drugs	8 (14.54)	624 (10.61)	0.3468
Trimethoprim	0 (0.00)	3 (0.05)	NA <sup>^</sup>
Warfarin	2 (3.64)	348 (5.92)	0.4744

a: Mean  $\pm$  Std. Dev & the T Test was used to compare continuous variables.  
\*: Significance at p value 0.05 as derived from T Test.  
b: n (%) & the Fischer's Exact Test were used to compare categorical variables.  
+: Significance at p value 0.05 as derived from Fischer's Exact Test.  
^: No P value calculated due to 0 sample size in hypoglycemia group.



**Table 4.6: Usage of Other Oral Diabetic Medications Stratified by Exposure to Hypoglycemia**

Concomitant Medications <sup>a</sup>	Hypoglycemia (N = 55)	No Hypoglycemia (N = 5879)	P-Value
Insulin	9 (16.36)	533 (9.07)	0.0060 <sup>+</sup>
Biguanides	37 (67.67)	3639 (61.90)	0.4139
Thiazolidinediones	11 (20.00)	950 (16.16)	0.4415
Alpha Glucosidase Inhibitors	1 (1.82)	16 (0.27)	0.0327 <sup>+</sup>
Meglitinides	1 (1.82)	11 (0.19)	0.0074 <sup>+</sup>
Dipeptidyl Peptidase 4 Inhibitors	505 (8.50)	5 (9.09)	0.8950

a: n (%) & the Fischer's Exact Test were used to compare categorical variables.  
<sup>+</sup>:Significance at p value 0.05 as derived from Fischer's Exact Test.

**Table 4.7: Descriptive Statistics Of Follow-Up Time, Stratified By Exposure To Hypoglycemia And The Effect Of Hypoglycemia On Sulfonylurea Medication Discontinuation**

Hypoglycemia Status	S. Size	Person Days Of Follow Up	Discont'd Patients	Crude HR (95% CI)	Adjusted HR (95% CI)
No Hypoglycemia	5,879	1789147*	1996	1.00 (REF)	1.00 (REF)
Hypoglycemia	55	12908**	20	1.47 (0.94 2.11) <sup>+</sup>	1.32 (0.82 1.88) <sup>++</sup>
<p>*Includes Time From Cohort Entry To Sooner Of Date Of Discontinuation, Date Of Hypoglycemia Or End Of Study Period.  **Includes Time From Cohort Entry To Date Of Hypoglycemia Exposure.  + Derived From A Time-dependent Exposure Cox Proportional-hazards Model With SU Medication Discontinuation As The Outcome Variable And Exposure Status As The Time-dependent Independent Variable.  ++Derived From A Time-dependent Exposure Cox Proportional-hazards Model Adjusted For Age, Gender, Number Of Medications, Insulin Use, Congestive Heart Failure, Cardiac Arrhythmia, Pulmonary Circulation Disorder, Peripheral Vascular Disorder, Diabetes (Complicated And Uncomplicated), Hypothyroidism, Renal Failure, Liver Disease, Coagulopathy, Deficiency Anemia, Depression, Retinopathy, Ulcer, Fluoroquinolones, Fibrates , Benzodiazepines, Biguanides, Tzd, AlphaglucoSIDase Inhibitors, Meglitinides.</p>					

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Appendix 1: Population Characteristics Of The Respondents With Diabetes Within

The MEPS 2008-2011

Variables	Unwtd Freq (4668)	Wtd %
<b>Age</b>		
18-34	204	4.37
35-49	816	17.48
50-64	1777	38.07
65 And Above	1631	34.94
Missing	240	5.14
<b>Gender</b>		
Male	2065	44.24
Female	2603	55.76
<b>Marital Status</b>		
Married	2619	56.11
Widowed/Divorced/Separated	1535	32.88
Never Married	514	11.01
<b>Income Level</b>		
Poor/Near Poor	1170	25.06
Low Income	782	16.75
Middle Income	1413	30.27
High Income	1303	27.91
<b>Education Level</b>		
Less Than High School	1381	29.58
High School	2068	44.30
Advanced Education	831	17.80
Others	370	7.93
Missing	18	0.39
<b>Race/Ethnicity</b>		
Hispanic	1042	22.32
White Non Hispanic	2221	47.58
Black Non Hispanic	1026	21.98
Others	379	8.12
<b>Percieved Health Status</b>		



Excellent/Very Good	1133	24.27
Good	1839	39.40
Fair/Poor	1696	36.33
<b>Insurance Coverage</b>		
Any Private	2624	56.21
Public Only	1562	33.46
Uninsured	482	10.33
<b>Insulin Use</b>		
Yes	1363	29.20
No	770	70.44
Missing	4	0.36
<b>MSA Status</b>		
NON MSA	833	17.84
MSA	3835	82.16
<b>Employment Status</b>		
Employed	2065	44.24
Not Employed	2599	55.68
Missing	4	0.09
<b>BMI Status</b>		
Under /Normal	646	13.84
Over	3923	84.04
Missing	99	2.12
<b>Smoking Status</b>		
Yes	647	13.86
No	3930	84.19
Missing	91	1.95
<b>Primary Care Provider</b>		
Yes	4299	92.10
No	342	7.33
Missing	27	0.58

Appendix 2 : Sample Panel Design For MEPS

**MEPS Panel Design: Data Reference Periods**

	2010				2011				2012			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
<b>Panel 14</b> Round 3 Round 4 Round 5												
<b>Panel 15</b> Round 1 Round 2 Round 3 Round 4 Round 5												
<b>Panel 16</b> Round 1 Round 2 Round 3 Round 4 Round 5												
<b>Panel 17</b> Round 1 Round 2 Round 3												
<b>Sample Size</b>	N = 31,228				N = 33,622				N = 37,182			

N is equal to the number of people with a positive person weight on the file.

Quality AfHRA. Medical Expenditure Panel Survey, Household Component, MEPS-HC Panel Design and Data Collection Process. 2013; [http://meps.ahrq.gov/mepsweb/survey\\_comp/hc\\_data\\_collection.jsp](http://meps.ahrq.gov/mepsweb/survey_comp/hc_data_collection.jsp). Accessed 01 September, 2014.

Appendix 3: List of Product Names For Sulfonylurea Medications

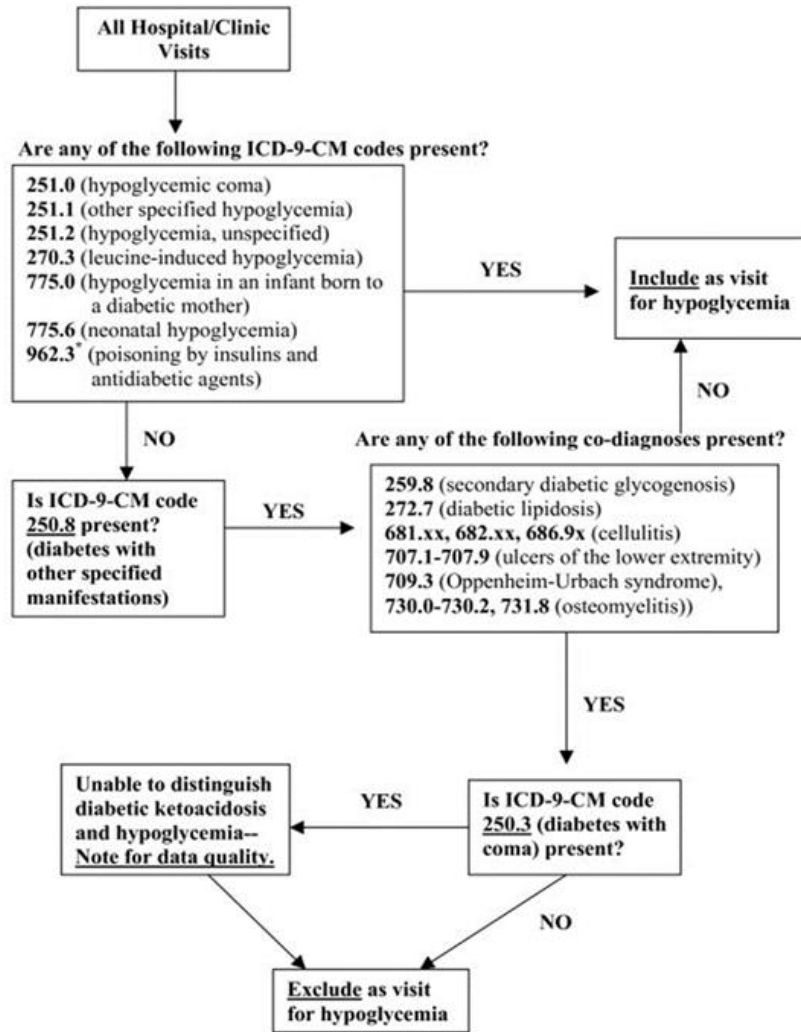
AMARYL  
AVANDARYL  
CHLORAL HYDR  
CHLORAMPHEN  
CHLORPROMAZ  
CHLORPROPAM  
DIABETA  
GLIMEPIRIDE  
GLIPIZIDE  
GLIPIZIDE ER  
GLIPIZIDE XL  
GLUCOTROL  
GLUCOTROL XL  
GLUCOVANCE  
GLYBURID MCR  
GLYBURIDE  
METAGLIP  
TOLBUTAMID

Appendix 4: Frequency OF Drug Episodes For The Study Population

Number of Drug Episodes <sup>a</sup>	Frequency	Percentage(%)
1	5408	55.72
2	2107	21.71
3	953	9.82
4	467	4.81
5	297	3.06
6	172	1.77
7	114	1.17
8	75	0.77
9	51	0.52
10	25	0.25
11	17	0.17
12	11	0.11
13	5	0.05
15	2	0.02

a: Separate episodes are defined by a gap of > 30 days between the end of days pf supply of the preceding prescription and refill of the next prescription

Appendix 5: Ginde and Colleagues-Algorithm to Identify Cases of Hypoglycemia



Ginde AA, Blanc PG, Lieberman RM et al. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. BMC Endocr Disord. 2008;8:4

**Appendix 6: Total Number Of Patients With First Episodes Of Hypoglycemia Within The Study  
Period Stratified By The Baseline And Post Baseline Timeline**

Study Timeline period	Hypoglycemia Frequency	Percentage(%)
Baseline Period <sup>a</sup>	139	36.68
Post-Baseline Period <sup>b</sup>	240	63.32

a: Baseline Period : 90 days starting from the first prescription of a sulfonylurea.  
b: Post baseline period : 9 months starting from the end of baseline period until the end of study period.

**Appendix 7: Frequency For Discontinuation Of Sulfonylurea Medication In The Eligible  
Sample Population**

Discontinuation Outcome	Frequency	Percentage(%)
Discontinuation <sup>a</sup>	5442	56.08
No Discontinuation	4262	43.92

a: Discontinuation : Defined as a gap of > 30 days between the end of days pf supply of the preceding prescription and refill of the next prescription

**Appendix 8: Frequency For Outcomes During The Study Timeline In The Eligible Sample  
Population**

Outcome	Frequency	Percentage(%)
Discontinuation <sup>a</sup>	5442	56.08
Censored <sup>b</sup>	184	1.89
End Of Study Period <sup>c</sup>	4078	42.03

a: Discontinuation : Defined as a gap of > 30 days between the end of days pf supply of the preceding prescription and refill of the next prescription  
b: Censored : Defined as an event of hypoglycemia occurring in the post baseline period.  
c: End of study period : Patients who were followed till the end of study period were free of the outcome of discontinuation or exposure to hypoglycemia within the post baseline period.

## Appendix 9: Charlson's Comorbidity Index

Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining Comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov; 43(11): 1130-9.

Myocardial Infarction: 410.X, 412.X

Congestive Heart Failure: 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.X

Peripheral Vascular Disease: 093.0, 437.3, 440.X, 441.X, 443.1--443.9, 447.1, 557.1, 557.9, V43.4

Cerebrovascular Disease: 362.34, 430.X--438.X

Dementia: 290.X, 294.1, 331.2

Chronic Pulmonary Disease: 416.8, 416.9, 490.X--505.X, 506.4, 508.1, 508.8

Rheumatic Disease: 446.5, 710.0--710.4, 714.0--714.2, 714.8, 725.X

Peptic Ulcer Disease: 531.X--534.X

Mild Liver Disease: 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 570.X, 571.X, 573.3, 573.4, 573.8, 573.9, V42.7

Hemiplegia Or Paraplegia : 334.1, 342.X, 343.X, 344.0--344.6, 344.9

Renal Disease: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.X, 583.0--583.7, 585.X, 586.X, 588.0, V42.0, V45.1, V56.X

Any Malignancy, Including Lymphoma And Leukemia, Except Malignant Neoplasm Of Skin: 140.X--172.X, 174.X--195.8, 200.X--208.X, 238.6

Moderate Or Severe Liver Disease: 456.0--456.2, 572.2--572.8

Metastatic Solid Tumor: 196.X--199.X

AIDS/HIV : 042.X--044.X

## Appendix 10: Elixhauser Comorbidity Index

Quan H, Sundararajan V, Halfon P, et al. Coding algorithms for defining Comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005 Nov; 43(11): 1130-9.

Peptic Ulcer Disease Excluding Bleeding: 531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9  
AIDS/H1V: 042.x--044.x  
Lymphoma: 200.x--202.x, 203.0, 238.6  
Metastatic Cancer: 196.x--199.x  
Solid Tumor without Metastasis: 140.x--172.x, 174.x--195.x  
Rheumatoid Arthritis/Collagen Vascular Diseases: 446.x, 701.0, 710.0--710.4, 710.8, 710.9, 711.2, 714.x, 719.3, 720.x, 725.x, 728.5, 728.89, 729.30  
Coagulopathy: 286.x, 287.1, 287.3--287.5  
Obesity: 278.0  
Weight loss: 260.x--263.x, 783.2, 799.4  
Fluid and Electrolyte Disorders: 253.6, 276.x  
Blood Loss Anemia: 280.0  
Deficiency Anemia : 280.1--280.9, 281.x  
Alcohol Abuse: 265.2, 291.1--291.3, 291.5, 291.9, 303.0, 303.9, 305.0, 357.5, 425.5, 535.3, 571.0--571.3, 980.x, V11.3  
Drug Abuse: 292.x, 304.x, 305.2--305.9., V65.42  
Psychoses: 293.8, 295.x, 296.04, 296.14, 296.44, 296.54, 297.x, 298.x  
Depression: 296.2, 296.3, 296.5, 300.4, 309.x, 311  
Congestive Heart Failure: 398.91, 402.01, 402.11. 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4-425.9, 428.x  
Cardiac Arrhythmias: 426.0, 426.13, 426.7, 426.9, 426.10, 426.12, 427.0-427.4, 427.6-427.9, 785.0, 996.01, 996.04, V45.0, V53.3  
Valvular Disease: 093.2, 394.x-397.x, 424.x, 746.3-746.6, V42.2, V43.3  
Pulmonary Circulation Disorders: 415.0, 415.1, 416.x, 417.0, 417.8, 417.9  
Peripheral Vascular Disorders: 440.x, 441.2, 441.4, 441.7, 441.9, 443.1, 443.9, 447.1, 557.1, 557.9, V43.4  
Hypertension, Uncomplicated: 401.x  
Hypertension, Complicated: 402.x-405.x  
Paralysis: 334.1, 342.x, 343.x, 344.0 344.6, 344.9  
Other Neurological Disorders: 331.9, 332.0, 332.1, 333.4, 333.5, 333.92, 334.x-335.x, 336.2, 340.x, 341.x, 345.x, 348.1, 348.3, 780.3, 784.3  
Chronic Pulmonary Ddisease: 416.8, 416.9, 490.x-505.x, 506.4, 508. 1, 508.8  
Hypothyroidism: 240.9, 243.x, 244.x, 246.1, 246.8  
Renal Failure: 403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585.x, 586.x, 588.0, V42.0, V45.1, V56.x  
Liver Disease: 070.22, 070.23, 070.32, 070.33, 070.44, 070.54, 070.6, 070.9, 456.0-456.2, 570.x, 571.x, 572.2-572.8, 573.3, 573.4, 573.8, 573.9, V42.7



## Appendix 11: Diabetes Complications

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Diabetes-related complexity

Macrovascular complications

Coronary artery disease: 410, 410.0, 410.00, 410.01, 410.02, 410.1, 410.10, 410.11, 410.12, 410.2, 410.20, 410.21, 410.22, 410.3, 410.30, 410.31, 410.32, 410.4, 410.40, 410.41, 410.42, 410.5, 410.50, 410.51, 410.52, 410.6, 410.60, 410.61, 410.62, 410.7, 410.70, 410.71, 410.72, 410.8, 410.80, 410.81, 410.82, 410.9, 410.90, 410.91, 410.92, 411.0, 411.1, 411.8, 411.81, 411.89, 412, 413, 413.0, 413.1, 413.9, 414, 414.0, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.1, 414.10, 414.11, 414.19, 414.8, 414.9

Congestive heart failure: 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 428, 428.0, 428.1, 428.9  
Arrhythmia 423, 423.0, 423.1, 423.2, 423.8, 423.9, 427.31

Stroke 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91

Peripheral vascular disease: 250.7, 250.70, 250.71, 250.72, 250.73, 440.2, 440.20, 440.21, 440.22, 440.23, 440.24, 440.29, 440.8, 440.9, 442.2, 442.3, 443, 443.0, 443.1, 443.8, 4438.1, 443.89, 443.9, 444.22, 444.81

Microvascular complications

Chronic renal pathophysiology: 274.1, 274.10, 274.11, 274.19, 403.10, 403.90, 404.10, 404.11, 404.90, 404.91, 581, 581.0, 581.1, 581.2, 581.3, 581.8, 581.9, 582, 582.0, 582.1, 582.2, 582.4, 582.8, 582.81, 582.89, 582.9, 583, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.8, 583.81, 583.89, 583.9, 583, 583.0, 583.1, 583.2, 583.4, 583.6, 583.7, 583.8, 583.81, 583.89, 583.9, 590.0, 590.00, 590.01, 593.6, 593.9, 753.12, 753.13, 753.14

Diabetic nephropathy: 250.4, 250.40, 250.41, 250.42, 250.43

Acute renal failure: 403.00, 403.01, 404.00, 404.01, 404.02, 404.03, 405.01, 453.3, 584, 584.5, 584.6, 584.7, 584.8, 584.9, 580, 580.0, 580.4, 580.8, 580.81, 580.89, 580.9, 590.1, 590.10, 590.11, 590.2, 590.3, 590.8, 590.80, 590.81, 593.81, 866, 866.0, 866.00, 866.01, 866.02, 866.03, 866.1, 866.10, 866.11, 866.12, 866.13

End-stage renal disease: V56.xx, 458.21, E87.91, V45.1

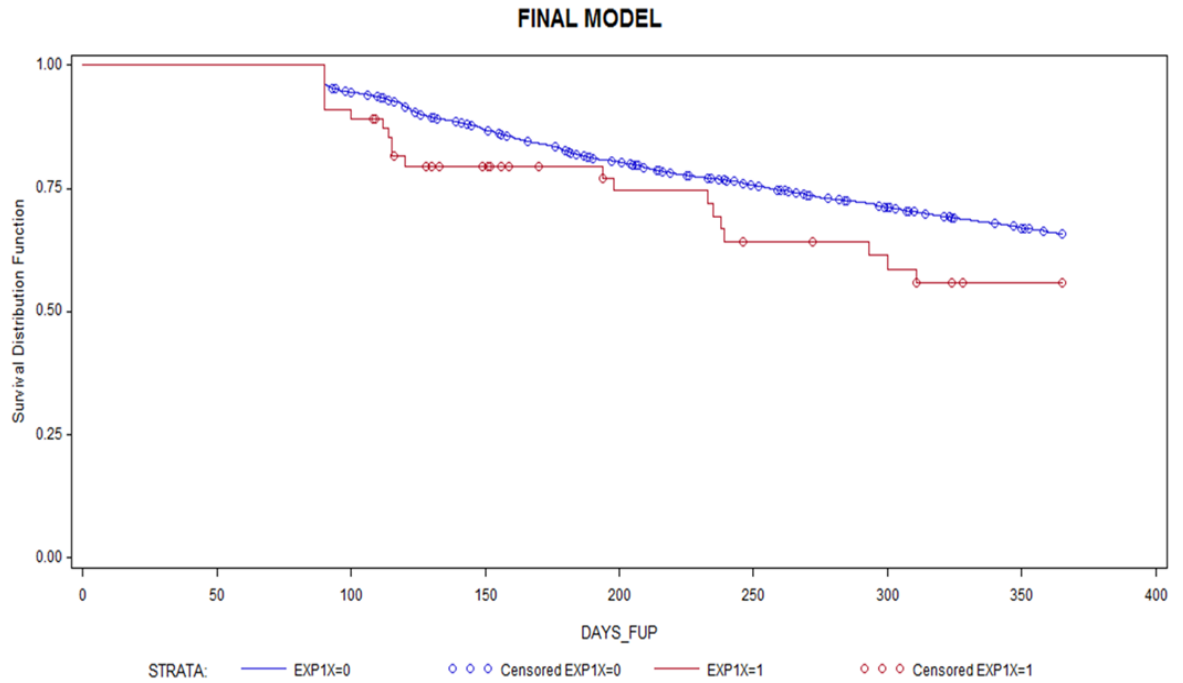
Dialysis: 389.5, 392.7, 394.2, 394.3, 399.5, 549.8

Diabetic retinopathy: 362.0, 362.01, 362.02, 250.50, 250.51, 250.52, 250.53

Ulcer: 700, 681.10, 681.11, 682.7, 707.1, 730.76, 730.77

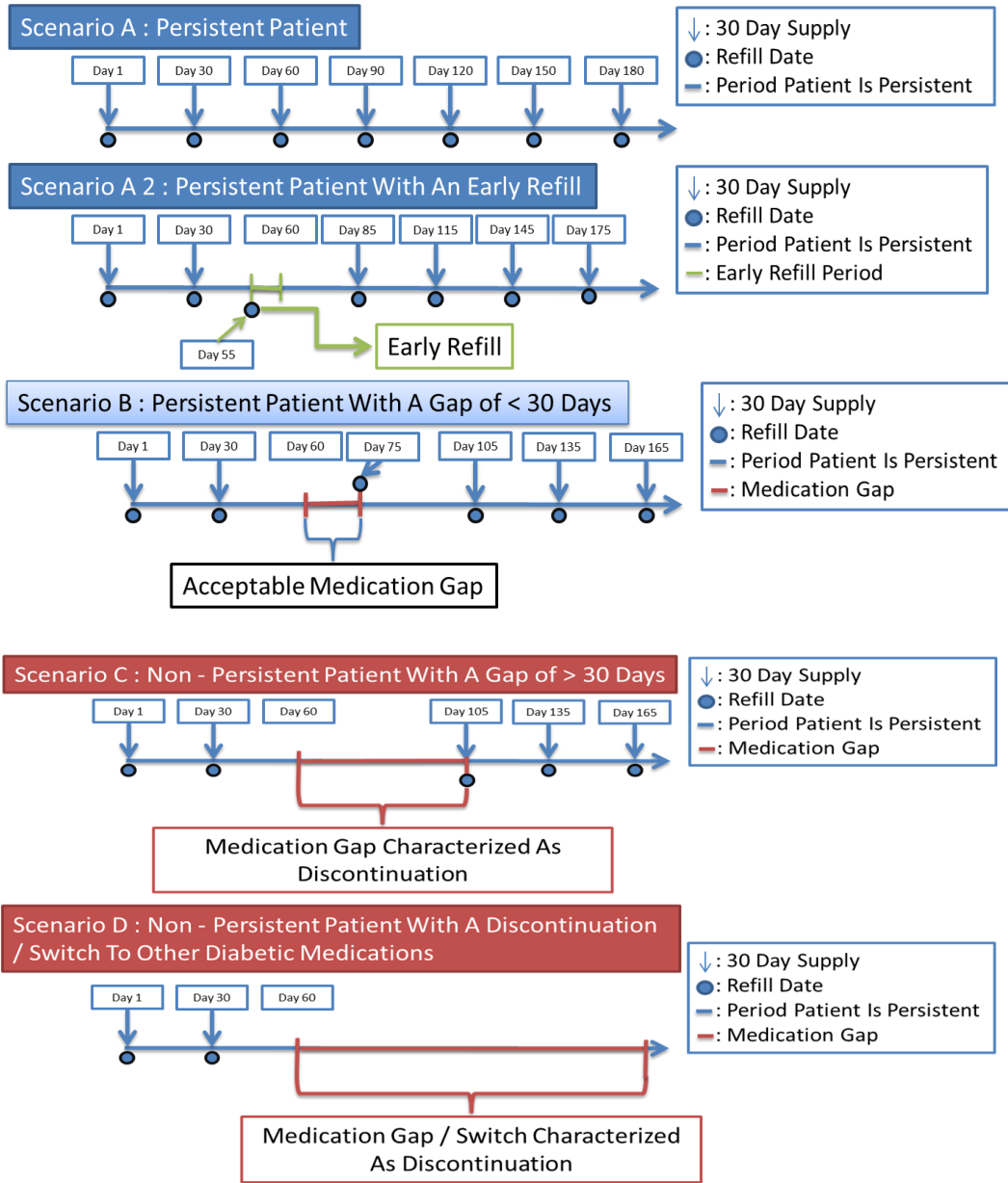
Amputation: 841.1, 841.2, 841.3, 841.4, 841.5, 841.6, 841.7, 841.8, 841.9

## Appendix 12: Testing the Proportionality Assumption

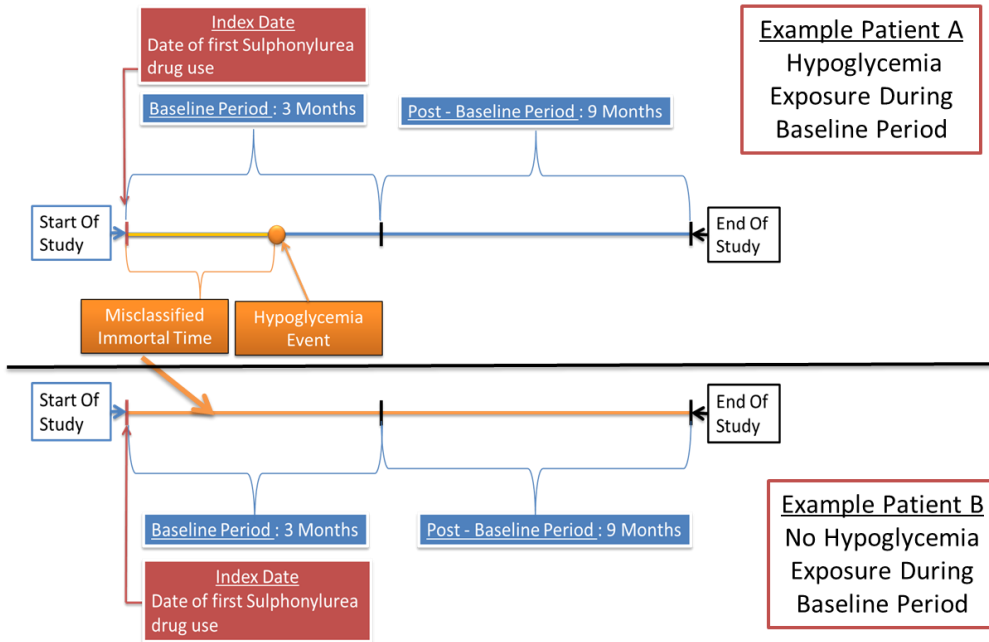


In the above figure, the curves do not cross each other thereby indicating that the assumption of proportionality is not violated. A time varying exposure variable was created in order to confirm this assumption and it could be seen that it reiterated the satisfaction of this assumption since it was insignificant.(a significant variable would indicate violation).

Appendix 13: Observed Scenarios For Medication Refill And Persistence Patterns



Appendix 14: Description Of Hypoglycemia Exposed And Unexposed Patients As An Example Of Classifying Immortal Time Bias As Unexposed Time.



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