IMPACT OF CHRONIC COMORBID ILLNESSES ON DIABETES CARE AMONG VETERANS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT OF THE DISSERTATION

IMPACT OF CHRONIC COMORBID ILLNESSES ON DIABETES CARE

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Clinical management of diabetes is complicated by chronic comorbidities. We examined the impact of close to 60 comorbidities on diabetes care, which were categorized into 5 chronic comorbid illness groups (CCIGs) based on degree of overlap/relatedness of their management plans with those for diabetes (Piette and Kerr framework): none (no comorbidity), concordant (very related, e.g. cardiovascular diseases), discordant (unrelated, e.g. mental/musculoskeletal illnesses), both concordant and discordant, and dominant (can overwhelm care priorities, e.g. metastatic cancer).

We conducted 5 separate analyses on cohorts of veterans with recent-onset diabetes who sought care at Veterans Health Administration (VHA) facilities nation-wide (95% male; average age 66 years) and hypothesized that having discordant/dominant illnesses would be associated with poor diabetes care, rapid rise in mean HbA1c levels following initial drop after treatment initiation for diabetes, lower adherence/persistence with diabetes medication regimens, and lower treatment intensification following diabetes treatment failure. Concordant illnesses presence was hypothesized to have limited or a positive impact on diabetes care.

We first evaluated association between CCIGs and diabetes care in a cohort of 42, 826 veterans with new onset diabetes in fiscal year (FY) 2003. Study outcomes were 5 guideline measures (HbA1c and LDL-C testing, diabetes-related visits, HbA1c < 8%, and LDL-C < 130 mg/dL) assessed in FY2004. Those with concordant illnesses received similar or better diabetes care compared to those with no comorbidities. Those with discordant and dominant illnesses received poorer care (odds lower by 10-21% and 32-54%, respectively).

The second analysis followed 79,249 veterans who initiated diabetes oral mono-therapy in FY2000-02 until they were censored at either the end of FY2010, death (28.6%), or lost to follow-up (5.8%). We compared HbA1c trends (992,196 tests) using piecewise linear random effects models. The models compared 3 HbA1c parameters: initial drop for first 6 months, HbA1c at end of 6 months, subsequent rise till end of study. Rate of rise of mean HbA1c was steeper for none (0.071%/year) and discordant CCIGs (0.081%/year). Rise in mean HbA1c for veterans with concordant (0.055%/year) and dominant (0.052%/year) illnesses were more moderate.

The third and fourth analyses (n=79,249) compared medication adherence (proportion of days covered (PDC) =>0.8) and non-persistence (treatment gap => 60 days) across CCIGs using logistic and Cox proportional hazards models, respectively. Half the cohort had PDC =>0.8. Discordant and dominant illnesses lowered odds for adherence by 12-32%. Dominant CCIG was more likely to be non-persistent [hazard ratio (95% CI)-1.12 (1.08-1.17)].

The fifth analysis utilized a cohort of 28, 472 veterans who failed initial diabetes treatment (first HbA1c > 8%). Treatment intensification (addition of second oral agent or insulin initiation) rates within 1 year of treatment failure were compared across CCIGs. Concordant and dominant CCIGs were associated with lower treatment intensification odds (by 10%).

In a large well-integrated managed care organization like VHA with limited access barriers, we found mixed support for the Piette and Kerr framework. Dominant illnesses lowered HbA1c regardless of inferior care processes, supporting need for patient-specific treatment goals to avoid complications from hypoglycemia. This questions the validity of HbA1c as quality measure for that group. Veterans with no or discordant comorbidities were associated with relatively lower adherence and poor maintenance of glycemic control, representing need for intervention via better care coordination. Strengths include large, population-based study with high prevalence of comorbidity. Key limitation is results not generalizable to the U.S. population.

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Chapter 1: Introduction

1.1 About Type 2 Diabetes Mellitus

Pathophysiology: Diabetes refers to group of metabolic disorders of varied etiology sharing a common manifestation of elevated blood glucose levels (or hyperglycemia) (1). Majority of the diabetes cases worldwide, approximately 90-95%, are caused by type 2 diabetes mellitus (also called as adult-onset (AODM) or non-insulin dependent (NIDDM)) (2-3).

The "triumvirate" of pathological mechanisms known to cause type 2 diabetes is: i) progressively increasing resistance to insulin in the liver; ii) progressively increasing resistance to insulin in muscle; iii) failure of pancreatic β-cells to secrete adequate insulin (4). Resistance to insulin in the liver (resulting in uninhibited hepatic glucose production) and muscle (leading to decreased glucose uptake) occurs first and manifests as postprandial hyperglycemia (elevated blood glucose levels following meals) (4, 5-8). The elevated circulating blood glucose levels trigger increased insulin secretion by β-cells of the pancreas to overcome insulin resistance and help maintain normal glucose tolerance. This phase continues till compensatory secretion of excess insulin by β-cells fails to catch up with increase in insulin resistance. With time, insulin secretion by β-cells declines due to their progressive failure (or burn-out), first leading to increased levels of postprandial glucose (impaired glucose tolerance), followed by increase in fasting glucose levels (impaired fasting glucose) also, and finally onset of type 2 diabetes (4, 5-13). The rate of progression to diabetes from impaired glucose tolerance is primarily linked to rate at which β-cell failure occurs (4).

Risk factors: Genetic predisposition is a major risk factor for developing insulin resistance (14). Due to genetic susceptibility individuals with family history of diabetes and those belonging to certain race/ethnicity groups (e.g. American Indians, Indians) are at greater risk for diabetes. Obesity and physical inactivity are associated with heightened insulin-resistance and accentuate risk of diabetes (15). Advancing age is associated with declining β-cell function thereby increasing risk of type 2 diabetes among older adults (4). Apart from diabetes, insulin resistance is an etiological factor for metabolic syndrome (or insulin resistance syndrome, syndrome X) as well, which comprises of: central adiposity, hypertension (increased blood pressure), dyslipidemia (elevated triglycerides and low density lipoproteins (LDL-C), decreased high density lipoproteins (HDL-C)), a pro-coagulant state, endothelial dysfunction, and increased risk of premature cardiovascular morbidity (1). Diabetes and metabolic syndrome often co-occur. In the United States (U.S.), about 87% of the adults with diabetes older than 50 years had concurrent metabolic syndrome (16).

Complications: Persistently elevated blood glucose levels cause bodily harm to the vascular system, which over time manifests as complications of diabetes (4). Diabetes complications are broadly classified as microvascular and macrovascular. The microvascular complications include diabetic retinopathy (visual impairment/loss) (17, 18), diabetic nephropathy (renal dysfunction/failure) (19), and diabetic neuropathy (mono-, poly-, autonomous neuropathy) (20). In the eye, kidney, and peripheral nervous system, chronic hyperglycemia results in intracellular accumulation of toxic factors (sorbitol, osmotic stress, advanced glycosylated end products (AGEs), and oxidative

stress), which over time leads to tissue destruction of microvascular system (4). On the other hand, damage to endothelium triggering atherosclerosis is the main pathological mechanism for macrovascular complications (4). Additionally, hyperglycemia is also associated with increased platelet adhesion and hypercoagulability (21, 22). These two mechanisms increase risk of macrovascular events, such as, sclerosis, occlusion, emboli, and infarction in the coronary arteries (coronary artery disease (CAD), angina, and myocardial infarction), peripheral arteries (peripheral artery disease (PAD), gangrene), and cerebrovascular arteries (stroke) causing significant cardiovascular-related mortality and morbidity (21, 22). Poor glycemic control is associated with excess risk for both microvascular and macrovascular complications. However, evidence for reduction in risk with improved glycemic control has been shown only for microvascular complications (23). There is suggestive evidence for reducing macrovascular complications with superior glycemic control among recent onset type 2 diabetes patients only (24, 25).

Diagnosis: The current American Diabetes Association's (ADA) criteria for diagnosis of type 2 diabetes are: i) HbA1c (or glycosylated hemoglobin, a biomarker for glycemic levels in prior 2-3 months) $\geq$ 6.5%, or ii) fasting plasma glucose $\geq$ 126 mg/dL (7.0 mmol/L), or iii) 2-hour plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT), or iv) random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia (26). ADA recommends that testing for diabetes should be done regardless of age when known risk factors are present to enable early detection. However for those with no known risk factors, testing is recommended only if they are 45 years or older. Depending on initial test results and risk

profile, individuals are advised to have follow-up tests within 3 years or earlier, in case of negative findings (26).

Treatment: Type 2 diabetes mellitus is a progressive illness which requires progressively intense and complex therapy interventions over patients' lifetime (3, 4, 22, 26, 27). Well-validated treatment algorithms recommend lifestyle changes (diet modification, exercise, and others) and mono-therapy with metformin at time of diagnosis, while monitoring of HbA1c levels every 3 months until meeting goal of HbA1c $\leq$ 7%. The monitoring intervals can be extended to once every 6 months as long as glycemic control (of $\leq$ 7% for most patients) is maintained (26). With time, as glycemic control deteriorates and HbA1c levels begin to rise (due to progressive insulin resistance and pancreatic β-cell failure) timely augmentation of therapy with additional anti-diabetic agents is recommended (22, 26, 27). Diabetic therapy augmentation choices, when mono-therapy with metformin fails, include dual or triple therapies, with addition of one or more oral hypoglycemic agents (OHA) and/or initiating insulin (27). These choices are partly influenced by patient's weight, risk for hypoglycemia, and degree of hyperglycemia (22, 26, 27). The major classes of anti-diabetic medications available for treatment are: biguanides (metformin), sulfonylureas, thiazolinidiones, alpha glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, apart from insulin (27).

Epidemiology: Diabetes is a fast growing global epidemic. The number of patients with type 2 diabetes worldwide is expected to rise from approximately 285 million in

2010 to around 440-550 million in 2030 (28-30). With an estimated 4.6 million deaths and USD 465 billion in healthcare costs worldwide for year 2011, diabetes imposes a significant disease burden on our society, the magnitude of which is only likely to increase further in the coming decades (28). As per the estimates from the Center for Disease Control and Prevention there were 25.6 million cases of diabetes (both diagnosed and undiagnosed) representing 11.3% of U.S. residents aged $\geq$ 20 years in 2010 (31). These estimates were higher (26.9%) among the elderly (> 65 years). The diabetes prevalence burden in the U.S. is projected to follow worldwide trends and increase to 44.7 million by year 2034 (30, 31). The annual incidence rate of diabetes is estimated to be close to 1%. Diabetes affects race-ethnicity groups differently and is more prevalent among non-Hispanic blacks (18.7%) compared to non-Hispanic whites (10.2%). Males have a slightly higher prevalence of diabetes than females, 11.8% vs. 10.8%, respectively (32). Diabetes and its complications present a huge public health challenge, the management and treatment of which is associated with huge economic costs. Diabetes is the leading cause of blindness, renal failure, and non-traumatic amputations (32). It is associated with 2-4 times higher rates of cardiovascular deaths and incidence of stroke compared to those without diabetes and reduces life expectancy by 5-10 years (32). According to the ADA, in the year 2007, the estimated total cost of diabetes care in the US was close to $174 billion, of which costs for direct medical care comprised of $116 billion (33). Costs resulting from loss of productivity due to diabetes-related morbidity and mortality were close to $58 billion. A major portion of health care expenditure in the U.S. is incurred for care of patients with diagnosed diabetes ($1 out of every $5 health

care dollars spent). The costs of health care among those with diagnosed diabetes were 2.3 times that of those without (33).

1.2 Comorbidity and diabetes mellitus

Chronic comorbidity, indicated by the presence of two or more concurrent chronic illnesses, is highly prevalent in the U.S., and affects about 75 million Americans with chronic illnesses such as diabetes (34-36). In 2004, about 90% of the respondents to the Medical Expenditure Panel Survey (MEPS) with diabetes reported having at least one additional chronic illness, while close to 15% reported having 4 or more, illustrating how common comorbidity is among the diabetes population (37). With an aging U.S. population, one can expect to see an increase in both the prevalence of diabetes and the proportion of diabetes patients with comorbidities. This is particularly relevant as diabetes patients with comorbidities may require more complex and coordinated care (38-40). Despite a higher prevalence of comorbidity among diabetes patients little is known about how comorbidities affect diabetes care. A big impediment to understanding the relationship between comorbidities and quality of diabetes care is lack of a reliable and validated measure for comorbidities. Prior studies that have looked at the impact of comorbidities used one or more of the following approaches: a) examined specific or related comorbidities (such as depression or mental illnesses) (41-44), b) indicated presence or absence of comorbidities, c) used comorbidity counts, and d) generated comorbidity indices using severity and number of conditions (such as Charlson comorbidity index (CMI) (45), Total Illness Burden Index (TIBI), and others) (46). Although widely used these approaches have many limitations: a) focus on specific and

or limited set of comorbidities doesn't permit the study of full impact of multimorbidity which is common among diabetes patients, b) use of comorbidity counts, although an easy approach, ignores differences between how illnesses interact with diabetes care, and their severity, and c) use of comorbidity indices originally derived for other outcomes, such as, predicting mortality (CMI), or resource utilization may not be appropriate for studying process measures and intermediate outcomes of diabetes care, d) most importantly none of the these approaches account for the fact that comorbidities might impact diabetes care differently depending on the degree to which their pathophysiology and management plans overlap with that of diabetes. Piette & Kerr (P&K) have proposed a novel theoretical framework as a way to categorize the effect of comorbidity on diabetes care in diabetes patients (47).

1.3 Piette and Kerr framework on competing demands (47)

Presence of comorbidities complicates diabetes management for patients, providers, and health care systems depending on the amount additional resources available for successful management of both diabetes and comorbidities. In the face of increasing prevalence of comorbidities, unless adequately staffed and resourced, health care systems can be overwhelmed by the magnitude of health maintenance activities (including screening, testing, counseling, and treatment) that need to be performed to ensure delivery of quality care to their patients. Providers are pressured to address a myriad of patient's problems within limited amount of time, in a given office visit. More often than not, particularly when patients' primary reason for the visit is unrelated to diabetes management, providers find it difficult to address all issues related to diabetes

management within a given patient-provider interaction. These issues are either put off for later visits or fail to receive full attention they deserve affecting the quality of diabetes care. Successful diabetes management is largely dependent on extent of patients' motivation and ability to self-manage. Presence of comorbidities can severely impact both these attributes. Comorbid illnesses such as mental illnesses, arthritis, low back pain, pulmonary diseases, and others can be major impediments to activities of self-care such as lifestyle changes and strict adherence to diabetes medication regimens and self-monitoring of blood glucose. Disease management of comorbidities in addition to diabetes places demands on the limited resources (social support, time, health care access, costs of visits, costs of medication, etc.). Patients who are burdened by comorbidities and have limited resources might be forced to prioritize their limited resources in favor of management of one chronic illness over the other.

Piette and Kerr's conceptual framework hypothesizes that disease management decisions and actions are driven by competing demands placed on the limited health care resources available to health care systems, providers, and patients. The framework expands on the competing demands model for primary care proposed by Jean et al (48) for delivery of clinical preventive services. This framework groups comorbid illnesses as: concordant illnesses (illnesses that share similar patho-physiological risk profile as diabetes with overlaps in disease management plans (e.g. cardio-vascular diseases)); discordant illnesses (illnesses with unrelated pathogenesis or management plans, e.g. mental health illnesses, musculoskeletal disorders); and dominant illnesses (illnesses whose severity eclipses all other illness management plans, e.g. end-stage kidney and liver diseases,

metastatic cancer). The framework hypothesizes that depending on nature of the comorbid illness various aspects of diabetes management may be either positively, un-, or negatively affected. For example, presence of concordant illnesses(s) might result in similar or better diabetes care as they are more likely to be the focus with similar disease management plans and being part of diabetes treatment guidelines. The presence of a discordant illness(s) on the other hand with limited overlap in disease management plans may actually end up drawing resources away from diabetes management and result in compromised diabetes care. Finally, presence of dominant illness(s) may result in substantially worse diabetes care as providers might be less aggressive with diabetes management perceiving limited benefits from preventing long-term diabetes complications in patients with short life-expectancy or are cognitively impaired to perform diabetes self-care.

1.4 Chronic comorbid illness groups (CCIGs)

Our first step was operationalization of the Piette and Kerr framework, which included identification of chronic comorbid illnesses for inclusion in our analyses. Selection of illnesses and their subsequent grouping into chronic comorbid illness groups (CCIGs) was done using a semi-nominative group process informed by Veterans Health Administration (VHA)-Department of Defense (DOD) Diabetes guidelines (49) and opinions of field-experts from multiple VHA centers (both internal and external to our study team). An extensive list of ~60 chronic illnesses was arrived at based on the team's belief that the management plans for these illnesses were reasonably likely to be synergistic or antagonistic with diabetes medication adherence and self-management

strategies of diabetes care. For our analyses, we categorized veterans with diabetes into five chronic comorbid illness groups (CCIGs): None (with no comorbid illnesses), concordant only, discordant only, both concordant and discordant, and dominant. Illnesses with treatment strategies concordant and synergistic with diabetes management were defined as concordant illnesses and included the following: macrovascular (coronary artery disease (CAD), cerebrovascular disease, peripheral vascular diseases (PVD), congestive heart failure (CHF)); microvascular (renal disease, advanced retinopathy, lower extremity complications). Apart from treatment synergies, presence of these illnesses was expected to be associated with more aggressive glycemic control (or intensification of treatment) given the known benefits in risk reduction with good glycemic control among these patients. The discordant illnesses included those that would likely interfere with or impede compliance with diabetes management, such as, gastro-intestinal illnesses affecting successful dietary modification; musculoskeletal, pulmonary, neurological illness limiting ability to exercise; mental illnesses and substance abuse affecting motivation and ability to self-manage diabetes care. The dominant illness group included those with limited life-expectancy (end-stage liver and kidney disease, malignant cancers except for skin cancers and prostate, and amputations). In addition, the dominant illness group included those who were cognitively challenged from dementia as they were deemed incapable of engaging in safe diabetes-related self-care. Veterans with no chronic illness other than diabetes were classified under none or no CCIG group. Presence of a dominant illness was given priority over other illnesses for CCIG classification. (See Appendix1 for listing of the chronic illnesses and the CCIG categories). We used the *International Classification of Diseases, Ninth revision, Clinical*

Modification codes **(**ICD-9-CM) codes to identify the chronic comorbid illnesses. We built on our research team's prior work for compilation of ICD-9-CM code list (50).

1.5 Overview of the study plan: This research effort entailed 5 tasks:

1. Operationalization of the conceptual Piette and Kerr framework (47) (discussed above)

2. Evaluation of the Piette and Kerr framework in real-world scenario using empirical data from a nationwide cohort of veterans with new-onset diabetes in fiscal year (FY) 2003. We examined differences in quality of diabetes-related care across the 5 CCIGs by comparing their guideline concordance in FY2004 for 3 process measures (HbA1c testing, diabetes-related office visit once every 6 months, and LDL-C testing once a year) and 2 intermediary measures (HbA1c <8% and LDL-C < 130 mg/dL). Our results supported Piette and Kerr framework's hypotheses that presence of concordant illnesses was associated with similar or better care, regardless of visit frequency. Discordant illnesses were associated with diminished care: an effect that decreases as visit frequency increases. The findings from this study are detailed in Chapter 2.

3. Assessment of the relationship between different types of comorbid illness groups and long-term glycemic control using longitudinal HbA1c trajectories. This study followed an index treatment cohort, comprised of veterans who newly initiated anti-diabetes medication therapy using mono oral agents in FY2000-02, till end of FY2010. The description of this study is detailed in Chapter 3.

We also examined 2 constructs related to glycemic control: medication compliance and treatment intensification, which are patient and physician-centered behaviors,

respectively. We hypothesized that these constructs would be impacted by type of comorbidity.

4. Using the same index treatment cohort (from Chapter 3), we assessed the relationship between comorbid illness groups and adherence and persistence with anti-diabetic medications. Adherence is defined as "the extent to which a patient acts in concordance with prescribed interval and dose of a dosing regimen", while persistence pertains to the time from treatment initiation to first treatment gap or discontinuity of treatment (51). The results from these studies are described in Chapter 4.

5. Finally, we studied how health care providers' responded to index treatment failure in presence of comorbidities. For this study we used as subset of the index treatment cohort, who failed mono therapy (defined as first HbA1c >8 % while being treated with index anti-diabetic medication). This study is detailed in Chapter 5 (Figure 1.1 and 1.2).

Key highlights of the significance of these studies:

1. Findings from our studies will help expand current knowledge on the interplay of comorbidity and diabetes care, an area of literature which is currently limited.
2. Use of novel theoretical framework for comorbid illness categorization, the Piette and Kerr framework (47).
3. Examination of an extensive list of comorbid illnesses.
4. Analyses of national-level, population-based data from nationwide cohort of veterans seeking care in a large managed care setting, the Veterans Health Administration.

1.6 Data sources

Data for the analyses was sourced from the Veterans Health Administration's (VHA) national level databases. The VHA has been a pioneer in implementation of the electronic health care records and database maintenance (52). The VHA is one of the largest integrated health care systems in the U.S., consisting of 152 medical centers, nearly 1,400 community-based outpatient clinics, community living centers, Vet Centers, and Domiciliaries, which provides comprehensive care to more than 8.3 million veterans each year (52). The VHA care facilities are organized into 21 Veterans Integrated Service Networks (VISNs). Veterans receive hospital-based care at the VHA medical centers for services such as critical care, surgery, orthopedics, mental health, physical therapy, radiology, pharmacy, and other additional services. The VHA is a pioneer in adopting computerization to support its health care mission. Data generated from delivery of routine medical care at each local facility is digitalized and is rolled-up to VISN and national level for storage in central data warehouses, which are used by hundreds of researchers for various types of health services research are extensively published. For the proposed studies, national level data was sourced from the following files (Table 1.1).

VHA National Patient Care Database (NPCD): The primary source of our data are the medical encounter data maintained at the Austin Automation Center (AAC). These data include patient treatment files (PTF), for inpatient and long-term care, and outpatient files (OPC). PTF record all inpatient and long-term stays at the time of discharge or at the end of the fiscal year for all patients currently in hospital (census files). OPC files record all outpatient visits with individual entries for visits at each

service or “clinic stop”. Both PTF and OPC provide information on patient characteristics, eligibility, and type of care, as well as multiple codes for procedures performed (ICD-9-CM and CPT4 codes (Current Procedural Terminology, 4th Edition (CPT 1999)) and diagnoses (ICD-9-CM codes) associated with care at each encounter or stay. The patient medical encounter data for the years FY1998-2010 were utilized.

VHA Decision Support System (DSS) Laboratory Data: VHA patient laboratory test results were available from the VHA Decision Support System (DSS), a national automated information system that integrates data from local VHA medical center clinical and financial systems for both inpatient and outpatient care. These files have test results for over 60 laboratory tests, including those used in our analyses. The files include test results from both inpatient and outpatient care and contain information on specific type of test, date of test, test result values, and units. We included DSS lab data from the years FY2000-10.

VHA Patient Pharmacy Data: Pharmacy data was obtained from 2 different sources. The main source for pharmacy data was the DSS pharmacy files from FY2003 onwards till FY2010. The DSS pharmacy files provided information on the name and dose of the specific medication prescribed, number of pills dispensed, number of days supplied, fill dates, and costs of medications. Though data is available from inpatient and outpatient services, determination of drug usage was obtained only from the outpatient records. Additionally, data from the Pharmacy Benefits Management Strategic Health Group (PBM), which maintains the VHA national prescription database, was used for years

FY1999-2002. Validation studies have shown close to 97% match between DSS and PBM pharmacy data records (53).

DEpiC database: The national VHA Diabetes Epidemiology Cohorts (DEpiC) is a research database of all VHA patients with diabetes since 1998 (54). It contains patient-level data on medical visits, with diagnoses and procedure codes for VHA and non-VHA care (from Medicare claims data), linked with VHA pharmacy and laboratory data, and with patient reported data from large national surveys. The first study evaluating the Piette and Kerr framework used the DEpiC data from FY2001-04. DEpiC data files were available for the years FY1998-2004 and were more complete by virtue of being a linked dataset with numerous sources of data.

Medicare: Majority of the veterans were eligible and were covered by Medicare, due to age and/or disability, and received part of their healthcare outside of the VHA. Linked Medicare data for VHA patients were available as part of DEpiC and were limited to FY1998-2004. Medicare claims data included Part A (institutional inpatient care) and Part B (physician care). Medicare data also provided data on lab tests performed but did not have results for those tests. No pharmacy data was available from Medicare during those years. Also, veterans seeking care at Medicare HMOs were excluded from the analyses as they do not report clinical data of their enrollees to Medicare.

VHA Corporate Data Warehouse (CDW): The CDW files were source for vitals status information (height, weight, and blood pressure) and date of death. The CDW is

national repository of data from several VHA clinical and administrative systems and is located at the Austin Information Technology Center with data from FY2000 onwards.

The raw data files were downloaded from their respective sources and were processed prior to data analyses. The data processing steps included running custom algorithms to translate character to numeric data, performing validity and range checks, fixing or excluding detectable errors in data, and excluding physiologically implausible values. Data for each veteran was fragmented and housed in different files originating from different data sources (medical encounter, labs, pharmacy, etc.). All available data for each veteran were carefully sorted and merged using a scrambled social security number into a single file for analyses.

Access to the VHA databases was facilitated through collaboration with Center for Health Care Knowledge Management, East Orange VHA in East Orange, New Jersey. The study was approved by the institutional review boards of both the VHA New Jersey Health Care System and the University of Medicine and Dentistry of New Jersey (now Rutgers, The State University of New Jersey) as exempt from Human Consent (HIPPA Waiver B). All data contain scrambled patient identifiers. The data were stored on password protected local area network (LAN) servers at the VHA facility in East Orange, New Jersey which can be accessed only through password protected and encrypted computer systems located in a locked, and alarm enabled room. These data were never stored on a local desktop machine, minimizing the likelihood of unauthorized access.

Study results were reported only for aggregated data that do not allow identification of individual veterans.

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Chapter II: Evaluation of Piette and Kerr framework

Note: This chapter is part of this dissertation effort that was published prior to the dissertation defense. Sri Ram Pentakota, the doctoral student, was the first and corresponding author on the publication (See Acknowledgement). Below is the reproduction of the published article with minor changes: "Pentakota SR, Rajan M, Fincke GB et al. Does diabetes care differ by type of chronic comorbidity? An evaluation of the Piette & Kerr framework. *Diabetes Care 2012; 35: 1285–1292*"

2.1 Background

Comorbid illnesses among patients may complicate care by competing for time, attention, and other resources (1-5). This is particularly applicable for patients with chronic illnesses such as diabetes mellitus (DM). As a consequence, the quality of diabetes care might be compromised unless additional resources are made available to compensate.

Comorbid illnesses are common among patients with DM. In 2004, 88.6% persons with diabetes who responded to the Medical Expenditure Panel Survey (MEPS) reported having at least one additional chronic illness, while close to 15% reported having 4 or more, illustrating how common comorbidity is among the diabetes population (2). The prevalence of both diabetes and comorbid illness is likely to increase as the U.S. population ages.

Despite a high level of comorbidity among diabetes patients, the literature studying the effect of comorbidity on diabetes care has predominantly focused on a single co-existing condition, such as a mental illness (6-9). On the other hand, researchers accounting for all

concurrent morbidity have applied aggregate morbidity counts or one-dimensional scores (10, 11). Both approaches fail to reveal the true impact of multiple comorbid illnesses, because not all illnesses are likely to have similar impact on diabetes care. Measuring patient comorbidity still poses a challenge to both clinicians and researchers as described in a recent article (12).

Piette & Kerr have proposed a novel theoretical framework as a way to categorize the effect of comorbidity on patients with diabetes and other chronic illnesses (13). The Piette & Kerr framework groups comorbid illnesses as: concordant (illnesses that overlap with diabetes in their pathogenesis and management plans (e.g. cardio-vascular diseases); discordant (illnesses with unrelated pathogenesis or management plans, e.g. mental health illnesses, musculoskeletal disorders); and dominant (illnesses whose severity eclipses all other illness management plans, e.g. end-stage kidney and liver diseases, metastatic cancer). The framework hypothesizes that effects differ, depending on the nature of the comorbid illness (13-15). The presence of a discordant illness may draw resources away from diabetes management and result in compromised diabetes care, the presence of a concordant illness may result in similar or better diabetes care, and the presence of a dominant illness may result in substantially worse diabetes care. The primary purpose of this study was to evaluate the relationship between diabetes care and different types of comorbid illnesses, classified by the degree to which their treatment is concordant with that for diabetes as described by Piette and Kerr. We hypothesized that having concordant illnesses would be associated with similar or better diabetes-related care outcomes, having discordant illnesses would be associated with worse diabetes-related care

outcomes and the presence of dominant illnesses would lead to substantially worse diabetes-related care outcomes.

2.2 Methods

Data Source

This study used data from the Diabetes Epidemiology Cohort (DEpiC), an administrative research database created by merging matched data files from the Veterans health administration (VHA) and Centers for Medicare and Medicaid Services (CMS). The DEpiC database identifies all VHA users with diabetes using a validated approach of having two or more diabetes-related ICD-9-CM codes (250.xx, 357.2, 362.0, and 366.41) from both inpatient and outpatient visits or any prescription for anti-glycemic medication using a 24-month window (16).

Study Cohort

A retrospective cohort study design was employed to study patients with incident diabetes in the DEpiC database (Figure 1.1 and 1.2). The study period extended from fiscal year (FY) 2001 to FY2004. The incident diabetes cohort comprised of patients with new-onset diabetes in FY2003. We chose to study patients with incident diabetes over those with prevalent diabetes because the former tend to be more homogenous with respect to diabetes duration and management needs/demands.

We identified patients with incident diabetes in baseline year (FY2003) by excluding those with diabetes-related codes and/or medications in a 2 year look-back period (FY2001-02). Comorbidities were identified using a minimum of two codes during the

look-back and baseline years. Data on number of laboratory tests performed were obtained from both VHA and CMS files, which allowed for enumeration of tests' frequency and consistency. However, the VHA Decision Support System (DSS) files were the only source for laboratory test results. Study outcomes were assessed in the follow-up year (FY2004).

From the DEpiC database, we identified 51,043 patients who were VHA system users throughout the study period (FY2001-04) and had new-onset diabetes in baseline year (FY2003). Patients enrolled in Medicare HMO plans (n=6,581) (whose clinical data are not reported to CMS) were excluded. Patients with less than 3 visits in baseline year (n=1,636) were also excluded to reduce potential under-assessment of comorbid illnesses. After the above exclusions, there were 42,826 patients with incident diabetes in the analysis cohort. Data was available on visits and testing for HbA1c and LDL-C for all 42,826 patients. However, results for HbA1c and LDL-C tests were available only for those patients who underwent laboratory testing in the VHA system. This reduced the cohort size to (n=39,516) and (n=39,332) when analyzing the intermediate measures, HbA1c <8% and LDL-C <130 mg/dL, respectively.

Study Variables

Outcome variables:

Our study assessed 5 diabetes-related care measures (3 process measures and 2 intermediate (or treatment goal) measures) that were based upon the Diabetes Quality Improvement Project (DQIP) measures (16): a test for HbA1c at least once every 6

months, a diabetes-related visit at least once every 6 months and a test for LDL-C at least once a year, HbA1c <8%, and LDL-C <130 mg/dL. We used the last test result in FY2004 from a subset of patients who underwent laboratory testing in the VHA system to assess our 2 treatment goal measures.

Independent variable:

Selection of relevant chronic comorbid illnesses and their subsequent grouping into chronic comorbid illness groups (CCIGs) was done using a semi-nominative group process informed by VHA-DOD Diabetes guidelines and opinions of field-experts from multiple VHA centers (both internal and external to our study team). We categorized patients using a comprehensive list of ~60 chronic illnesses into the five CCIGs: no comorbid illness, concordant only, discordant only, both concordant and discordant, and dominant. Patients with no illnesses other than diabetes belonged to the none CCIG group. Presence of a dominant illness was given priority over other illnesses for CCIG classification. See Appendix1 for listing of CCIGs and the ICD-9-CM code list used to identify them. We built on our team's prior work for compilation of ICD-9-CM code list (18). The variable CCIG was our main independent variable.

Covariates:

We included health care utilization and socio-demographic variables available in the database as covariates. Face-to-face (F2F) visit frequency was used to measure overall and diabetes-related visits. F2F refers to in-person visits to a medical professional with decision-making capacity in either the Medicare or VHA outpatient services and were

identified using the current procedural terminology (CPT) codes for visits as outlined in the healthcare effectiveness data and information set (HEDIS) measures (Appendix1 lists CPT codes used to define F2F visits). The visits were classified as being diabetes-related if they were assigned a diabetes-specific ICD-9-CM code (250.xx) for the given visit. Total F2F visits were categorized as: less than 7, 7-12, 13-24, and more than 24 visits per year.

Socio-demographic variables included: age categories: under 55 years, 55-64 years, 65-74 years, and over 75 years; gender; race/ethnicity divided into: White, African American (or Black), Hispanic, and Other; marital status: married or not married; and VHA priority status: low income, severely disabled, moderately disabled, and co-pay. The VHA priority status is derived from VHA enrollment group assignment based on assessment of an individual's income and service-connected disability.

Statistical Analyses

We first cross tabulated study covariates with CCIGs and diabetes care (study outcomes) to describe their bivariate associations and to identify potential confounders. Second, we tabulated the proportion of patients who met care guidelines across the CCIGs in the overall cohort and within each F2F visit frequency stratum. Third, logistic regression modeling was used to test for association between CCIGs and diabetes care, sequentially without (model 1) and with (model 2) socio-demographic variables (age, gender, race, marital status, and income). Model 3 added visit frequency to model 2. In model 4, we tested for interaction between CCIGs and F2F visit frequency to determine the effect of

visit frequency on the strength of association between CCIGs and diabetes care. We assigned each veteran to a parent facility where they had the most outpatient encounters. We then used this information to adjust for the effects of clustering by VHA facility. Patients belonging with no comorbidity were used as the reference category in all our logistic regression models. We report odds ratios (ORs) and their 95% confidence intervals (CIs). Analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). PROC GENMOD was utilized for the modeling and the CONTRAST option was used to generate odds ratios for the interaction terms.

2.3 Results

Only 20% of the 42,826 patients were free of chronic comorbid illnesses. Patients with concordant illnesses constituted ~13% of the study cohort; 30.13% had discordant illnesses and 25.15% had both concordant and discordant illnesses. About 12% of patients were diagnosed with a dominant illness (Table 2.1).

All covariates were significantly associated with type of comorbidity (chi-square p-value < 0.001 for all associations). Diabetes patients with either no comorbidities or those with discordant illnesses were more likely to be younger, female, and non-white (Table 2.1). The highest proportions of patients who were married (66.66%) and categorized as those with low-income (38.03%) or Co-pay (28.40%) for priority status (i.e. low disability burden) were seen in the concordant CCIG. The discordant group had the lowest levels in all these categories (56.06%; 31.36%; 12.59%). A service-connected disability, as measured by the VHA priority code, was more prevalent among patients with discordant and dominant illnesses. F2F visits increased as comorbidities increased. The annual F2F

visits ranged from mean (SD), 7.85(6.6) for the group with no illnesses to 17.48 (15.1) for those with both concordant and discordant illnesses and 17.29 (15.5) for the dominant CCIG (Table 2.1).

All study covariates showed statistically significant bivariate associations with study outcomes and were entered into the multivariable logistic regression models. Table 2.2 displays the unadjusted proportions of patients who met diabetes-related care guidelines and treatment goals by CCIG's and visit frequency. About forty-four percent got tested for HbA1c once every 6 months in FY2004. Three out of four (71%) patients met the HbA1C goal of <8%. The LDL measures were met at a higher rate (LDL-C testing 77.2% and LDL < 130 mg/dL 60.7%). Fifty-eight percent of the study cohort had a diabetes-related visit once every 6 months as recommended. For all the diabetes-related care measures, the proportion of patients meeting them increased as F2F visits increased. Comparing across CCIGs, the highest proportions were almost always observed in either none or the concordant CCIG and lowest in dominant CCIG.

Table 2.3 presents results from 3 sequential main effects models built to assess the association between CCIGs and the five study outcomes (unadjusted; adjusted for socio-demographic covariates; and additionally adjusted for F2F visit frequency). Results from the unadjusted models (Model 1) showed that comorbidity type was associated with odds of meeting diabetes-related care guidelines and goals. Increased odds were seen among concordant and both CCIGs. Discordant and dominant groups were associated with similar and lower odds, respectively, for meeting diabetes-related care guidelines and goals compared to no comorbidity group. For example, patients with concordant illness had 17% higher odds for getting tested for HbA1c as per guideline compared to those

with no comorbidity (OR (95% CI), 1.17 (1.09-1.25)); and patients with both concordant and discordant comorbidities had 8% higher odds. The dominant group had 29% lower odds of meeting the guideline. This trend was seen for two other outcomes: annual LDL-C testing and LDL-C < 130 mg/dL goal. Model 2 additionally controlled for socio-demographic variables and the results were similar to Model 1. The initial models showed a pattern of improved or similar diabetes care among patients with either concordant, discordant or both illnesses, contrary to the study hypotheses.

However, after adjusting for differences in F2F visit frequency, model 3 results supported the study hypotheses. For all study outcomes, patients in the concordant illness group had similar or increased likelihood of meeting recommended diabetes-related care measures compared to those with no illnesses, except for diabetes-related F2F visit. Those with discordant and dominant illnesses reported statistically significantly lower likelihood of meeting recommended diabetes-related care measures. The odds for positive study outcomes were reduced by 10% to 21% among patients in discordant illness group compared to 54% to 32% for those with dominant illnesses.

Table 2.4 presents results from model 4 which included all covariates from model 3 along with an additional interaction term between CCIG's and face-to-face visit frequency. The interaction term was significant for four out of five outcomes (HbA1c goal, LDL-C goal, LDL-C testing, and diabetes-related visits), indicating that the association between CCIGs and study outcomes by was modified by visit frequency.

Presence of concordant illnesses was associated with similar odds for HbA1c-related measures regardless of visit frequency and increased odds for LDL-related measures only

at lower visit frequency (< 24 visits). Presence of discordant illnesses resulted in lower odds for HbA1c-related measures when annual visit frequency was 12 or lower and for LDL-related measures with fewer than 7 annual visits. Presence of dominant illnesses was associated with significantly lower odds for HbA1c-related measures regardless of visit frequency and LDL-related measures when number of visits made in a year were 24 or lower. For all illness groups, the odds for having diabetes-related face-to-face visit as recommended were significantly lower than those with no illnesses regardless of visit frequency.

Using results from the LDL-C goal measure (LDL-C level < 130 mg/dL) as a specific illustration: among patients who had less than 7 visits per year, having concordant illnesses significantly increased the odds (1.16 (1.01 -1.33)) of meeting the goal compared to patients with no comorbidity. The odds were significantly lower for patients with discordant (0.87(0.79-0.96)) and dominant illnesses (0.52(0.45-0.61)).

As visit frequency increased to 7-12 annual visits, those with concordant illnesses had significantly higher odds of meeting goal (1.38(1.20-1.60)). Those with both concordant and discordant illnesses also had higher odds (1.21(1.06-1.38)). Those with discordant illnesses only had lower odds (0.95 (0.85-1.07)) but the findings were not statistically significant. Those with dominant illnesses had lower odds (0.72 (0.61-0.86)). These results were similar among patients with 13-24 annual visits.

Finally, among patients making more than 24 annual visits, there were no statistically significant differences among the 5 CCIG's in the odds for attaining the LDL-C goal.

2.4 Discussion

In the initial analysis, our study found that an increasing burden of comorbidity was associated with increased visit frequency and higher levels of receiving recommended diabetes-related care regardless of type of CCIG. However, after adjustment for visit frequency, the results supported the study hypotheses that having concordant illnesses was associated with similar or better diabetes care; having discordant illnesses was associated with decreased diabetes care; and the presence of dominant illnesses resulted in the markedly decreased diabetes care. This difference was more pronounced among patients who made less frequent visits.

There are some studies that reported a similar relationship between comorbidity type and receipt of guideline-concordant care: among post-acute myocardial infarction patients in Sales et al (19) and hypertensive patients in Lagu et al (20). Krien et al showed that chronic pain affected hypertension care in diabetes (21). Our findings support the underlying premise of the competing demands framework proposed by Piette and Kerr (13) among veterans with new-onset diabetes. Healthcare resources are finite and diabetes patients burdened with additional discordant or dominant illness may not be able to receive all the care they need to address both their diabetes and non-diabetes needs (13, 22).

However, the phenomenon of competing demands was not consistent. As visit frequency increased, differences in diabetes care became less pronounced. Healthcare systems' ability to compensate in this way will depend on availability of resources, including subspecialty care and care coordination. Physicians' capacity will depend on how well he or she manages visit time to address multiple illnesses. Finally, patients' ability to compensate may depend on access to healthcare, the availability of a caregiver, and how

they prioritize their self-care (13-15, 22-24). Such compensatory mechanisms are a likely explanation for the association between increased comorbidity burden and a seemingly paradoxical improvement in quality of care that has been reported in several studies (11 25-28).

Few other studies have reported a similar interaction between type of comorbidity and visit frequency when examining quality of care. Kodl et al reported that among veterans, when visit frequency was not accounted for, presence of a mental health diagnosis was associated with either increased or similar likelihood of receiving colo-rectal cancer screening. However, after adjusting for visit-frequency, presence of a mental health diagnosis increases risk of not receiving colo-rectal cancer screening (29). Along similar lines, Fenton et al demonstrated substandard preventive care for diabetes among HMO-enrolled patients who made either infrequent outpatient visits (less than 8 per year) or more frequent but low-priority visits (30).

We identified two studies of patients with diabetes that were based upon the competing demands framework proposed by Piette and Kerr (13) and whose results failed to support the framework's hypotheses. Woodard et al studied the effect of concordant and discordant illnesses on quality care among all veterans with diabetes (31). They concluded that complexity of comorbidity was associated with superior care, regardless of comorbidity type. Their results remained unchanged after accounting for visit frequency. The difference between their study and ours is that their sample included patients with prevalent as well as incident diabetes, used different comorbid illnesses to determine CCIGs, and used the relative risk score from the diagnostic cost groups (DxCG) as an illness burden indicator. DxCG is correlated with both comorbidity type

and visit frequency and its inclusion might modify the effect of the other variables. Bayliss et al used a population of prevalent diabetes patients to study the pre- and post-effect of three discordant incident conditions (cancer, depression, and exacerbation of chronic obstructive pulmonary disease (COPD)) on intermediary outcomes (HbA1c, LDL-C, and blood pressure) and reported no short-term or long-terms effects on study outcomes (32).

Our implementation of the Piette and Kerr framework can refine the assessment of comorbidities when evaluating diabetes care. In studies of pay-for-performance, for example, risk adjustment for diabetes-related comorbidities measured them in aggregate, whereas our findings indicate that different types of comorbidities have different effects. It can also be used to evaluate the adequacy of the compensatory response across health care systems, wherein adequate compensation is more likely to attenuate the adverse effect of discordant comorbidities. It might also help in identifying system-level factors that favor adequate compensation such as better care coordination. Additional applications might include evaluating whether diabetes care quality measures need tailoring for certain illness groups.

Our study has several strengths. First, we employed a large population-based study cohort to evaluate the Piette & Kerr framework. Second, we used a comprehensive list of ~60 comorbid illnesses. Third we evaluated five CCIG groups including those with dominant illnesses. Fourth, the VHA population is known to have higher prevalence of comorbidity which enabled us to successfully contrast the patterns of study outcomes across the various CCIGs, which might not possible in populations with low prevalence of

comorbidity. Fifth, use of a longitudinal study design preserved temporality between the exposure and outcome.

Our study has several limitations. First, the study results are not generalizable to the U.S. population or other populations, as the VHA population is predominantly male and has a high prevalence of comorbidity. Second, we did not have access to laboratory results from Medicare. Data from private insurance was also unavailable. Third, the inclusion criteria in the baseline year (FY2003) biased the study to those with at least 3 or more face-to-face visits. Fourth, our study cohort was drawn from an administrative database which doesn't include any patient reported data on resources available for self-care of diabetes management; health care access barriers; knowledge, attitudes, beliefs, perceptions on diabetes care; quality of patient-physician interaction; and other factors which are known to have an impact on our study outcomes. Fifth, when classifying comorbid illnesses we only looked for presence or absence of comorbid illnesses. We did not account for their severity. Sixth, we classified all patients into broad CCIG's but didn't assess the relative burden of individual illnesses within each CCIG.

Further research is required to extend this study's findings. One such area is the impact of type of visits (primary or specialty) on diabetes care. Also, this study is limited to understanding the impact of the framework on diabetes care for those with new-onset diabetes. We feel that further analysis will be required to determine whether these findings will apply to those with prevalent diabetes as well.

Comorbidity type and visit frequency affected diabetes care. Discordant illnesses were associated with decreased diabetes care, possibly due to competition for time, attention,

and other limited resources. Concordant illnesses, on the other hand, were associated with either similar or better care, probably because their management is congruent with that for diabetes. Dominant illnesses were associated with significant decrease in diabetes care that may be appropriate given their poor prognoses. Additionally, the effect of competing demands was greater at the lower end of the visit frequency spectrum. This suggests the need for better care-coordination within health care systems to improve diabetes care among patients with comorbidities. The Piette and Kerr framework, based upon the competing demands model can be used as a tool to compare diabetes care across health care systems and providers; identify patient groups who might be receiving over- and under-treatment and design specific interventions to improve their care; design appropriate performance measures based on evidence-based benefits while accounting for individuals' comorbidity type and life expectancy.

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Chapter III: Type of chronic comorbidity and long-term glycemic control

3.1 Background

Results from randomized clinical trials (RCTs) (1-10), considered as gold standard for evidence generation, have been the mainstay for guiding recommendations/policy-making on diabetes care practices (11-13), particularly among patients with incident diabetes. This practice persists despite the known limitation of poor generalizability of findings reported by RCTs. RCTs enrollees tend to be younger and have less comorbidity than those in the general population (14-18). Additionally, very few RCTs are designed for long-term follow-up, due to prohibitive costs and challenges with retention of trial participants (15). Chronic comorbidity is quite prevalent in the general diabetes population and is known to impact diabetes care (14, 17, 18). However, there have been few studies examining the impact of comorbidity on long-term diabetes care, of which glycemic control is one key component. Real-world population-based retrospective cohort studies using large administrative-databases enable us to study long-term trends in glycemic control vis-à-vis' chronic comorbidities with far fewer resources (costs, personnel, time, etc.), lengthier follow-up times, and generate more generalizable results. Findings from such studies will help fill critical knowledge gaps in current literature and guide practice guidelines and policy-making towards interventions that are more effective, patient-centered, and relevant to multitude of diabetics with chronic comorbidities.

We took advantage of the extensive databases of the Veteran's Health Administration (VHA) to examine patterns of long-term glycemic control, using HbA1c trends, among veterans who recently initiated anti-diabetes medication therapy. In particular, we were interested in assessing if there was a relationship between comorbidity type and patterns of glycemic control (19, 20). We grouped comorbidities relative to degree of overlap between their patho-physiology and management plans and goals vis-à-vis diabetes care into: concordant (e.g. cardiovascular illnesses, have high degree of overlap); discordant (e.g. mental, musculoskeletal, are unrelated or may be impeding); dominant (e.g. metastatic cancer, end stage renal disease, comorbidities that might eclipse management of other illnesses) (19). We hypothesized that, relative to veterans who have no comorbidities, glycemic control would be similar or better among veterans with concordant illnesses and worse among those with discordant and dominant illnesses. The purpose of this study was to compare patterns of long-term glycemic control (using HbA1c growth curves/trajectories), across various comorbidity groups relative to those with no comorbidities. We further explored if this relationship differed by age groups.

3.2 Methods

Data Source

The Veterans Health Affairs (VHA) system is the nation's largest integrated healthcare system, providing care for over 8 million veterans annually (21). The VHA has been a pioneer in implementation of the electronic health care records and database maintenance (22). We utilized the VHA's administrative, clinical, pharmacy, and laboratory files; linked them to create a national cohort of veterans who recently initiated anti-diabetic

medication therapy. We used the Pharmacy Benefits Management (PBM) (fiscal years (FY) 1999-2002) and Decision Support Systems (FY2003-2010) pharmacy databases for pharmacy data; HbA1c values were obtained from the laboratory files of Decision Support systems (FY2000-2010), National Patient Care Data (FY1998-2010) files were used as sources for diagnosis and procedure codes to assess comorbidities and utilization, and Central Data Warehouse files (FY2000-2010) provided vital stats data.

Study Design

Retrospective cohort study design was used to study longitudinal HbA1c trends. The study period ranged from FY1998-2010 (Figure 1.1 and 1.2). The index event for inclusion in the study was initiation of anti-diabetic therapy with a single oral medication (mono-therapy), either metformin or a drug from the Sulphonylurea (SU) or Thiazolinidione (TZD) drug class in FY2000-02 (Oct 1st, 1999 to Sep 30th, 2002). The study follow-up began from the date of initiation of anti-diabetic therapy and extended until end of FY2010, death, or loss to follow-up, whichever occurred earlier. A study veteran was determined to be lost to follow-up and was censored when there was no clinical activity (visits, labs, medication refills) for over an 18-month interval. Depending on the index date, study veterans' maximum duration of follow-up ranged between 8 and 11 years.

Study cohort

Study cohort selection began with enumerating veterans whose index (or first) prescription for any anti-diabetic agents, oral or injectable (HS501 and HS502 VHA drug

class codes) was in the period between FY2000-02 (n=428,948), with no anti-diabetic agent prescriptions for at least 12-months prior. Applying our index event definition, we identified 267,271 veterans whose index anti-diabetic agent was either metformin or an agent from the Sulphonylurea (SU) or Thiazolinidione (TZD) drug class. Veterans with no data on HbA1c test results or ICD-9-CM codes, for the study period, were excluded and after this exclusion we were left with 241,150 veterans. Our final analytical cohort included veterans who had at least one ICD-9-CM 250.xx coded (code for diabetes) visit in baseline year and one visit during the two years prior to baseline year (n=79,249) (Figure 1.1 and 1.2).

Outcome variable

The outcome variable was test result values for HbA1c, which were analyzed as a continuous measure. Our analyses included a total of 992,126 repeated measures of HbA1c test results for study veterans measured between FY2000-2010. For inclusion in the analyses we restricted HbA1c values falling within biologically plausible range of 3-18%. HbA1c tests within 30 days of the previous test were excluded as HbA1c reflects the status of glycemic control for the prior 90-120 days and HbA1c tests repeated within shorter intervals tend to be similar. All remaining HbA1c test results, following these exclusions, were used in our analyses. The last HbA1c test result recorded within 180 days prior to and 30 days after the index date was assigned the baseline HbA1c, wherever available. About one-third of our study veterans (n=26,422) did not have a baseline HbA1c and for them baseline HbA1c was recorded as a missing value and were included in the analyses.

Primary Exposure variable

We categorized up to 60 chronic comorbidities primarily into 5 chronic comorbid illness groups (CCIGs) - none (with no comorbidity), concordant only, discordant only, both concordant and discordant, and dominant. The CCIG classification was based on the type of comorbidities and the degree to which their disease management overlaps with that of diabetes. The chronic comorbidities were identified using ICD-9-CM diagnoses and procedure codes from the outpatient and inpatient clinical files. Ascertainment of comorbid illness' presence and CCIG assignment was done initially at baseline and was repeated annually during the study follow-up. At each assessment, clinical data from the corresponding prior 3 years (1 baseline year and 2 look-back years) was used to identify comorbidities, defined by presence of 2 or more codes. A comorbid condition was considered present regardless of being prevalent or incident. Incident comorbidity data from subsequent annual assessments were used to update the CCIG categorization wherever necessary (e.g. none CCIG was updated to concordant CCIG with incidence of concordant comorbidities in later assessments and so on). Dominant illnesses were given precedence over other CCIGs when more than one type of comorbidity was present. Given the long duration of study follow-up we expected that the study veterans would experience onset of additional comorbidities during the study period, which would change their CCIG status. Our primary exposure variable reflected baseline CCIG and the final CCIG from the last year of observation, unique to each study veteran. The final CCIG_CCIG variable had 9 exposure groups as follows - none_none (when both baseline and final CCIG were none), none_other (when baseline CCIG was none and the final

CCIG was either concordant, discordant, both, or dominant), concordant-concordant, concordant_other, discordant_discordant, discordant_other, both_both, both_other, and dominant. As mentioned before, presence of dominant illnesses took priority in the CCIG assignment process and hence, those categorized as dominant at baseline did not get updated to other CCIGs despite possible incidence of other comorbidities. CCIGs were updated only if incident illnesses were from a different CCIG group. The CCIG status remained unaltered if the incident illnesses belonged to the prevalent CCIG.

Covariates

All socio-demographic variables (categorical in nature) were assessed at baseline and were not updated during study follow-up and hence were analyzed as time-invariant variables. They included: Age groups (under 55, 55-64, 65 to 74, and 75 years or more); race/ethnicity (Whites, African-American (or Black), and Other); Gender (male/female); and marital status (married/not married). VHA priority code was used as a socio-economic status indicator, which is assigned based upon income levels and degree of service-connected disability. The priority code variable had 4 levels: co-pay, low income, moderately disabled, and severely disabled. Observations with missing data were marked as missing and retained in our analyses.

Baseline HbA1c was adjusted for in the models as a 5-level categorical variable: <7%, 7-<8%, 8-<9%, =>9%, and missing. Prior studies have reported significant seasonal variation in HbA1c test results (23, 24). To minimize the impact of seasonal variations on HbA1c trajectories, we used the sine and cosine terms to account for yearlong

seasonality-related variability using 12-month fluctuation cycle (25). The use of sine along with the cosine function is a common application in mathematical modeling to model periodic cyclical fluctuations. The sine and cosine terms were computed based on the HbA1c tests' date relative to Oct 1, 2001 and varied for each HbA1c observation. Two variables were used to account for body-mass-index (BMI). The baseline BMI was included in the analyses as a 5-level categorical variable: normal/underweight (<25), overweight (25 to <30), obese (30 to <35), morbidly obese (=>35) and missing. Additionally, we adjusted for the annual change in BMI from baseline, with a one year lag, as continuous measure. The change in BMI was computed as BMI in previous year minus the BMI at baseline.

Our prior work has shown that comorbidity type and utilization frequency interact with one another to affect quality of diabetes care. To account for utilization we counted the number of face-to-face visits, both overall and those with 250.xx ICD-9 code, made to the VHA in each of the follow-up years. Face-to-face (F2F) variable was defined as the number of visits to a health-care professional with decision-making capacity following the healthcare effectiveness data and information set (HEDIS) definitions (See Appendix1 for list of CPT codes used to define F2F visits). We used 2 F2F visit variables: non-diabetes related and diabetes-related. The non-diabetes related F2F variable (Non-DMF2F) was used as a categorical variable with 4 levels: 0-4, 5-8, 9-12, >12 visits and was time-variant in nature. Those F2F visits with a 250.xx ICD-9-CM code were classified as diabetes-related face-to-face visits (DMF2F) and were included in the analyses as a three-level categorical variable: 0-2, 3-4, >4 visits and was also time-

variant in nature. Number of non-DMF2F and DMF2F visits made in previous year was applied when analyzing impact of visits on HbA1c in a given year.

Another time-varying categorical variable described type of anti-diabetic medication (oral only, both oral and insulin, insulin only). It was assessed annually and was updated with a one year lag similar to other time-varying variables. As a proxy for comorbid illness severity, a variable that looked at the different classes of medications (apart from anti-diabetic) used for other chronic illnesses, for each veteran was developed and used as a time-varying covariate with a one-year lag. The variable was a sum of non-diabetes medication classes prescribed annually and was categorized as <=4, 5-8, 9-12 and over 12.

Statistical Analyses

We used means, medians, and proportions to describe the baseline characteristics of the study cohort, selected utilization patterns and glycemic measures, and their relative distributions across the comorbidity groups. Using graphs, we explored glycemic control trends for the overall cohort and exposure or CCIG groups by plotting the unadjusted quarterly mean HbA1c values (Figure 3.1). To adjust for correlation of the data due to repeated measures of HbA1cs overtime for each study veteran, we chose random effects models (aka random coefficient models, hierarchical linear models, individual growth models, multilevel modes, mixed models (26)) to evaluate HbA1c trajectories (or growth curves) and their relationship with CCIGs. A random effects model (the full model) with time variables (in months), CCIG, and all aforementioned independent variables, including socio-demographic variables, baseline HbA1c, seasonality terms, non diabetes-

related face-to-face visits, diabetes-related face-to-face visits, baseline BMI, annual change in BMI, diabetes medication, and selected interaction terms was fitted and compared to a model (the unadjusted model) with only the time variables. We were especially interested in evaluating whether longitudinal patterns of HbA1c values differ by CCIG groups. We ran piecewise random effects models using two time variables: i) time between diabetes treatment initiation and first 6 months (slope AB) and ii) time from end of 6 months to last observed HbA1c (slope BC). Point B (the intercept) was the join-point of the two slopes representing HbA1c value at the end of 6 months. The two time variables were introduced both as main terms and were also interacted with CCIG in our models. The choice of piecewise modeling was dictated by the distinctly non-linear pattern of HbA1c trends following diabetes treatment initiation (sharp drop for initial 6 months followed by a gradual rise for rest of the study period), which we wanted to highlight and examine further for differences across the CCIGs; mean HbA1c values for all CCIGs more or less hit nadir around the 6-month period before beginning to rise following the initial drop); attempts to fit simple linear models using quadratic terms for time resulted in very poorly fit models. Stratified analyses were conducted using the adjusted model in the 4 age group strata. We evaluated various variance-covariance structures for the random effects models, specifically, compound symmetry and various spatial correlation structures (e.g., spatial-power, spatial-exponential, spatial-Gaussian, etc.) to describe the serial correlation of repeated HbA1c measurements for each veteran (27). We also evaluated the inclusion of a random intercept variable in the model. We report results from models that used spatial-power variance-covariance structure with random intercepts as this provided the best Goodness-of-fit statistic, AIC. Graph of the

adjusted quarterly HbA1cs for the comorbidity groups was plotted using the predicted HbA1c values generated from the adjusted piecewise random effects model runs (Figure 3.2). A two-sided alpha of 0.05 was used as level of significance for statistical tests. All analyses were done using SAS v.9.2 software. We used SAS PROC MIXED procedure step to run the random effects model. To test robustness of our study findings, we repeated the analyses in the following sub-cohorts: with baseline HbA1c values (any value), baseline HbA1c >7%, baseline HbA1c > 8%, and with those who survived till end of FY2010. The first 3 sensitivity analyses allowed us to examine if the relationship between comorbidity and HbA1c trends qualitatively differed with different inclusion criterion. We compared results from our primary analyses with those from the sub-cohort who survived till the end of study period to assess the impact of mortality on our study results.

3.3 Results

Of the 79,249 study veterans, close to 40% or 33,567 had no comorbidities at baseline (none_none and none_other) of which about ~75% experienced an additional incident illness (none_other) during study follow-up. Discordant CCIGs (28%) (discordant_discordant and discordant_other) was the second largest comorbidity group at baseline, followed by concordant and both (~12% each). Dominant illnesses were prevalent in only ~6% of the study cohort at baseline. In the overall cohort, the median length of follow-up was 8.5 years (Q1-Q3: 5.3-9.6) with a mortality rate of about 29%. Death rates were higher amongst those in concordant groups [concordant-concordant 42.5% & concordant-other 35.3%], both groups [both-both: 41.4% & both-other: 51.1%],

and dominant (54.8%) CCIGs compared to ~20% amongst none and discordant groups. Median follow-up years were significantly lower in concordant_concordant (6.2) and dominant CCIG (6.0) while for rest of the groups it was between 7.5 and 8.8 years.

As shown in Table 3.1, CCIG groups varied in their socio-demographic characteristics as well. Veterans with no or only discordant comorbidities at baseline were more likely to be younger, female, non-White and not married. On the other hand, veterans with concordant illnesses were older and had higher proportion of males, White, married patients. Burden of service-connected disability was greater amongst those with discordant illnesses. Proportion requiring a co-pay were higher amongst those belonging to none and concordant CCIGs.

For the overall cohort, the unadjusted mean (s.d.) HbA1c level at initiation of anti-diabetic medication was 8.07% (1.98%). Those with no comorbidities [none-none: 8.11% (2.08%) & none-other: 8.23% (2.09%)] had higher baseline HbA1c levels, followed by the two discordant illness groups (8.12%). Amongst the remaining CCIG groups, baseline HbA1c ranged narrowly between 7.79% and 7.90%. These differences were statistically significant (ANOVA p-value <0.001).

There was significant variation in the utilization of clinical services across the CCIG groups, measured by frequency of diabetes and non-diabetes related face-to-face visits. Overall, the ratio of diabetes to non diabetes-related visits in the baseline year was 2:5. Variations in baseline year diabetes-related visit frequency were not that pronounced. The

median frequency for diabetes-related visits was 2 (Q1-Q3: 1-3), compared to only 1(Q1-Q3: 1-2) amongst veterans with no additional comorbidities. However the variation of non diabetes-related visits was more pronounced, with the median number of non diabetes-related visits at 5 (Q1-Q3: 2-10). Patients with discordant, both concordant and discordant, and dominant illnesses had far more non diabetes-related visits than those without comorbidities.

Table 3.2 provides statistics on average annual visits, diabetes and non diabetes-related visits, and HbA1c tests during follow-up period by the CCIG groups. The results showed the following: a) frequency of visits, both non-diabetes and diabetes-related, was disproportionately low in two CCIGs- the none_none and concordant_concordant; b) frequency of HbA1c tests was also lower in these two CCIGs; c) despite relatively higher frequency of visits, frequency of HbA1c tests in dominant CCIG were comparable to those in none_none and concordant_concordant CCIG; d) in groups where there was an incident comorbidity, we found an increase in both types of visits and HbA1c tests. For example the concordant_other group had median annual visit frequency of 6 and 3, for non-diabetes and diabetes-related visits, respectively compared to 2 and 4 in the concordant_concordant group; e) level of glucose control was inconsistent in the discordant groups (i.e. higher proportion of veterans with extreme HbA1c values (18% and 12% with at least one HbA1c <6% and =>9%, respectively).

We observed differences in longitudinal HbA1c trends across comorbidity groups. Table 3.3 presents results from the regression analyses using piecewise random effects models.

Results from the unadjusted model and the adjusted model were quite similar and hence we discuss the latter alone here.

In our adjusted model, for the reference group (none_none CCIG), following initiation of anti-diabetic medications, the value of mean HbA1c initially dropped (slope AB) at rate of 2.338% units/year for the first 6 months, hit a nadir of 7.13% at end of 6 months (or Point B), and subsequently rose incrementally (slope BC) at rate of 0.073% units/year till end of study. Significantly faster drop in HbA1c was observed only in the discordant_discordant groups' mean HbA1c values (2.510% units/year). The concordant and both groups' mean HbA1c dropped at slower pace than none_none group (between 2.005 and 1.939%/year) during first 6 months. At point B or at end of 6 months following treatment initiation for diabetes, the mean HbA1c (6.946%) for the discordant_discordant CCIG was the lowest compared to all other groups. Only two other groups, discordant_other and dominant CCIG had lower mean HbA1c levels than those belonging to none_none group. All other CCIG groups' mean HbA1c level was higher than that for the none_none group. From the 7^{th} month onwards, following initiation of anti-diabetes medication, and till end of study observation, shown as the annualized slope BC (Post 6 months) in the Table 3.3, the mean HbA1c values increased in a relatively linear fashion across all CCIGs but rose at a different pace within each CCIG. The discordant_discordant CCIG, which had the steepest initial decline paradoxically also, had the steepest rise (0.085% units/year). In fact, it was the only CCIG whose mean HbA1c values increased more precipitously than those for the reference group (none_none). The mean HbA1c values for veterans in the both_other CCIG increased at

the slowest rate (0.044% units/year). The two concordant groups, both-both, and none-other group performed similarly (~0.06 units/year).

Analysis by Age Group:

Table 3.4 presents results from our stratified analyses within the 4 age groups. Across all the age groups, the mean HbA1c trajectories for the various CCIGs followed similar non-linear trends as observed in the overall cohort. Relative differences in mean HbA1c trend estimates between the none_none group and other CCIGs, in the youngest age group (under 55 years), for most part replicated the results seen in the overall cohort. The only exception being that in the under 55 year cohort, the none_none group's rate of ascent of mean HbA1c levels outpaced all other groups, including discordant_discordant. With increase in age, the direction of differences persisted but the magnitude of differences diminished to becoming less or non-significant. Using the results from the none_none group across the 4 age categories, it is clear that the youngest veterans have the worst glycemic control of all ages. Compared to younger veterans (under 55 years), the older veterans (75 years or older) had lower baseline HbA1c [7.58 vs. 8.60%]; had a gradual initial descent in mean HbA1c values following anti-diabetic medication initiation [1.562 vs. 3.126% units/year]; reached lower HbA1c mean value at end of 6 months from treatment initiation [6.684 vs. 7.031%]; had a moderate rate of rise in mean HbA1c values following the initial drop [0.042 vs. 0.115% units/year].

Sensitivity Analysis

As part of sensitivity analyses, we conducted the analyses in sub-cohorts of veterans with non-missing baseline HbA1c values, baseline HbA1c values greater than 7% and 8%, and with those who survived till end of study period. In all these sensitivity analysis, we found that there few qualitative differences in the results compared to our primary analyses and would lead to drawing similar inferences regarding relationship between comorbidity groups and HbA1c trends, thereby indicating robustness of our study findings (Table 3.5).

3.4 Discussion

In this study we examined the association between type of chronic comorbidities and long-term glycemic control in a diabetes treatment initiation cohort that was followed for a maximum of 11 years, using longitudinal HbA1c trajectories. In our observational study of HbA1c trends, over a 10-year period; we found that following anti-diabetic treatment initiation, the trajectory of HbA1c takes a non-linear curvature, regardless of type of comorbidity. Immediately following medication initiation, mean HbA1c values dropped at a brisk pace for the first 6 months before bottoming out, following which they change course and gradually rise for the remainder of the study follow-up. We also found that veterans in the VHA system respond to increased comorbidity burden by augmenting resource utilization (through more frequent visits and tests).

We found mixed support for our hypotheses in our study findings. Veterans with concordant illnesses were initiated with anti-diabetes medication therapy earlier (or at lower HbA1c levels) compared to those with no additional illnesses other than DM. The

discordant illness groups' baseline HbA1c values were comparable to those without comorbidities despite having higher visit frequency.

Following medication initiation (slope AB), the concordant groups' mean HbA1c dropped less precipitously for first six months and ended at slightly higher value when compared to the group of veterans with no comorbidity. Contrary to our expectations, the discordant groups' mean HbA1c values declined faster. Possible explanations for the divergence of these findings from our study hypotheses: a) it is highly probable that veterans with concordant illnesses might have already initiated life-style modifications (diet, exercise, etc.) as part of their concordant illnesses management efforts and hence the incremental realizable gain from initiation of anti-diabetic medication therapy might be lower than expected in these groups; b) on the other hand, among veterans with discordant illnesses initiating anti-diabetic medication therapy might be their first intervention targeted at lowering glucose levels and to which they seem to initially respond better than other groups, however, this effect appears to be short-lasting, perhaps due to lower levels of adherence; c) veterans with discordant illnesses were much younger than those with concordant illnesses and hence might be more responsive to treatment.

A strong support for our study hypothesis was seen during the period following the first 6 months after treatment initiation. Compared to the group with no comorbidities, the discordant_discordant groups' mean HbA1c rose at a quicker pace (0.085%/year vs. 0.073%/year), indicating that presence of discordant illnesses was associated with poorer

long-term glycemic control. The opposite was observed for the concordant_concordant group which had a more moderate rate of rise of HbA1c levels following the initial drop (0.059%/year vs. 0.073%/year) compared to the group with no comorbidities, At the end of the study period, the mean HbA1c values for veterans with discordant illnesses was slightly higher than for those with concordant illnesses. These findings support our hypothesis that presence of concordant illnesses, whose management plans overlap with that for diabetes, does not negatively impact long-term glycemic control, unlike with discordant illnesses.

Our findings didn't support our hypothesis that those with dominant illnesses will have much worse glycemic care compared to none CCIG. This was the group with highest mortality rate (54.8%). It is possible that these patients with terminal illnesses tend to be lot sicker and lose weight rapidly, which is known to be independently associated with reduction in HbA1c.

Type of incidence comorbidity also appeared to impact long-term glycemic control. Comparison of groups with and without additional incident comorbidities during study period showed that: glycemic levels rose less briskly when a concordant/dominant illness was incident in a group with only discordant comorbidities (0.068%/year vs. 0.085%/year, respectively); dominant illness onset in those with existing concordant and discordant illnesses reduced rate of rise of mean HbA1c values (0.044%/year vs. 0.057%/year); glycemic control was similar among veterans belonging to the two concordant groups (concordant_concordant and concordant_other), i.e. the additional

incident illnesses had minimal impact on the HbA1c trends, when prevalent illnesses were concordant by nature.

There is limited literature on findings from population-based, cohort studies that have examined long-term glycemic control trends among incident diabetes cohorts (diagnosis/treatment) and almost none that primarily examined the impact of chronic comorbidities. The patterns of HbA1c trajectories reported by us were consistent with those seen in participants of the United Kingdom Prospective Diabetes Study (UKPDS) clinical trial (3, 4). In the UKPDS trial newly diagnosed diabetes patients were randomized to receive either conventional (diet alone) or intensive (oral anti-diabetic agents and insulin) and were followed for an extended period of time. The initial dip was greater in the intensive therapy arm compared to the conventional therapy arm (drop in mean HbA1c values was 2.90% vs.2.00%, respectively) (3, 4, 28). There have been several reports on longitudinal glycemic control in various prevalent diabetes populations (29-32). Prevalent diabetes cohorts tend to have chronic and advanced diabetes with complex treatment regimens unlike patients in our treatment initiation cohort; therefore our results are not directly comparable. Richardson et al reported that mean HbA1c levels were higher by 0.13% units in patients with depression compared to those without (29). Study of veterans with prevalent diabetes showed poor glycemic control among Non-Whites compared to Whites (30, 31). A ten year follow-up study of prevalent diabetes patients from a hospital network reported a decrease in mean HbA1c values by 0.4% (1.8%) (32). Our study design also differs from those longitudinal studies that have trended mean HbA1c values over time in dynamic populations, using repeated cross-

sectional measurements, such as, the ones using repeat national survey data (33,34). Contrary to our findings these studies have reported a decrease in mean HbA1c values over time, suggesting improved quality of diabetes care. Some of the differences can be explained by the influx of healthier, recently diagnosed diabetes patients with lower HbA1c values into the cohorts, early diagnoses due to increased screening for diabetes, change in guidelines (aggressive cut-off values) for diagnoses and treatment, amongst others.

Use of a large administrative database allowed us to study several sub-groups over a protracted period of time, which is not feasible with RCTs. Population average measures on smaller sample might have drowned out significant differences between sub-groups, the findings of which can have implications for policy-making and care delivery practices. We were able to identify sub-groups who are probably being under-treated and/or over-treated, who might benefit from patient-centered care that is tailored to better meet their needs. Those with none and discordant illnesses who tend be younger, be Non-White, more disabled, and have longer life-expectancy represent a missed opportunity. These patients might benefit if they are started on medications sooner and are managed more aggressively to slowdown the pace of the rise of HbA1c with better care coordination. Amongst those with dominant illnesses we could probably recommend less stringent control based on evidence-based analyses of tradeoffs, while accommodating patients' needs and expectations. Such measures might help prevent unwarranted episodes of hypoglycemia and related morbidity and mortality burden.

We used national level, population-based, long-term (~10-years), retrospective, observational data on a large-sized cohort of veterans, who initiated anti-diabetes medication therapy in FY2000-02. Unlike clinical trials, our cohort included all study-eligible veterans, regardless of their comorbidity status. High prevalence of comorbidity among veterans and the availability of rich clinical data in the VHA databases for their valid assessment enabled us to describe and contrast chronic HbA1c trends by comorbidity groups. Application of relatively novel taxonomy and use of extensive list of chronic comorbidities (close to 60) are unique to our study. We used an appropriate methodology, piecewise random effects models, to study non-linear longitudinal HbA1c growth curves across comorbidity groups while simultaneously accounting for random variation within-individuals using repeated HbA1c measures. With random effects models we were able to use all HbA1c measurements available in our dataset and also account for time-constant and time-varying variables. Our study was unique in that it accounted for comorbidity status at baseline and for incident comorbidity during the study years. We also accounted for an extensive list of covariates that we believe could have confounded our study results.

Our study has a few limitations that need to be considered while interpreting our study findings. The VHA population is predominantly male, older, and sicker, limiting generalizability of our results to the general US population. The data didn't permit for reliable assessment of comorbid illness severity and a proxy variable measuring the number of medication classes was instead used. Our analyses didn't include clinical data for those veterans who additionally utilized either Medicare or private insurance for

certain health care services. The lack of non-VHA data resulted in under-assessment of comorbidity burden and possible misclassification of the exposure or comorbidity group categorization. However, since comorbidity was updated annually during study follow-up, the degree of misclassification might not be sufficiently large enough to impact study results. Finally, there was very little overlap in the F2F visit frequency distribution between CCIGs. It is unclear if the model completely accounted for the confounding effect of excess visits in select groups. The VHA is a highly integrated health care system with limited barriers to access and is known to provide quality care to all veterans (35-37). Differences between the comorbidity groups might have been more pronounced in other health care settings which are less integrated and have greater barriers to care. Our study results could be biased due to informative censoring, introduced by possible relationship between high or low HbA1c values and mortality. As a result HbA1c values could be an under (or overestimated), particularly in groups with higher mortality rates and in the later years of the study.

We have examined role of chronic comorbidities on long-term glycemic trends and found differences based on type of comorbidity. Diabetes patients with concordant illnesses, compared to those with no other illnesses have shown better glycemic control, despite having comparable frequency of resource utilization. Those with discordant illnesses have comparable or worse glycemic control despite utilizing the system two- to three-fold compared to those with only diabetes. Those with dominant illnesses tend to have lower HbA1c values, which are probably more related to their comorbidities than quality of diabetes care.

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Chapter IV: Type of chronic comorbidity and medication adherence and persistence

4.1 Background

Non-compliance with prescribed diabetes medication regimens is a major barrier to successful reduction and maintenance of glycemic levels at or below target levels. Prior studies have shown an association between poor adherence and inadequate glycemic control (1, 2), increased morbidity and mortality outcomes (3, 4), and excess health care costs and utilization (5, 6). In 2009, the National Quality Forum (NQF) endorsed several measures on medication management, one of which included assessment of adherence to diabetes medications (7, 8).

Numerous methods are available for assessment of medication adherence/persistence: patient surveys/self-reports, pill counts, direct observation of medication taking, electronic monitoring, measuring drug or metabolite levels, and pharmacy refill data (the most indirect of all measures) (9-14). Use of pharmacy refill data, enables assessment of medication adherence and persistence in large patient populations with minimal time and labor inputs; is known to yield valid results that are well correlated with those using more direct measures; is common in field of pharmaco-epidemiology (10, 14). Medication adherence (or compliance) and persistence measures capture two separate constructs of patients' behavior pertaining to use of prescribed medications. Adherence is defined as "the extent to which a patient acts in concordance with prescribed interval and dose of a dosing regimen", while persistence pertains to the time from treatment initiation to first treatment gap or discontinuity of treatment (15).

Very few prior studies have examined the relationship between chronic comorbidities and their impact on diabetes patients' adherence and persistence with their prescribed diabetes medications. The purpose of this study is to assess whether there is an association between type of chronic comorbidity and adherence and persistence to their diabetes medications in a cohort of veterans who recently initiated diabetes medication therapy. We hypothesized that compared to veterans having no comorbidities, having concordant illnesses would be associated with similar or better adherence, veterans with discordant illnesses would be associated with lower adherence, and those with dominant illnesses would be associated with even lower diabetes medication adherence rates. Similarly, we hypothesized that compared to veterans without comorbidities, veterans with concordant illnesses will be more or equally persistent with their diabetes medications, and on the other hand veterans with discordant and dominant illnesses will have lower persistence levels.

4.2 Methods

Data Source / Study Design / Study Cohorts

Analytical cohorts for the medication adherence and persistence analyses were drawn from the cohort of 79,249 veterans who were part of HbA1c trends study and utilized the same data sources used in our prior analyses. These veterans were members of a cohort that initiated diabetes medication therapy, using a mono oral agent, between FY2000-02 (Figure 1.1 and 1.2).

For the medication adherence analyses, we included 77,466 out of 79,249 veterans who had at least 2 pharmacy refill records. Veterans with only 1 pharmacy refill record were excluded as it was not possible to compute medication adherence for those veterans. The length of the observation period was specific to each veteran, beginning from date of diabetes treatment initiation to date of death, or loss to follow-up, or September 30th, 2010, whichever came first. Loss to follow-up was defined as inactivity in the VHA pharmacy files for more than one and a half years.

For the persistence analyses all the 79,249 veterans from the HbA1c trends study were included in the analyses. The length of study period was limited to the first 24 months following diabetes treatment initiation. Veterans were censored as of date of death or date of last activity if they were lost to follow-up before the end of first 2 years. We limited the study to the first 24 months following treatment initiation to identify early non-persistors, who are most likely to be consistently non-persistent in later years and might benefit from timely intervention. Another reason for limiting the persistence analyses to first 24 months was that when follow-up was extended till end of FY2010 (~10 year follow-up) almost all veterans (~90%) were non-persistent with their diabetes medications at least once, regardless of comorbidity (Figure 4.1).

Outcome variables

Adherence was measured using the proportion of days covered (PDC) method and applying prescription-based approach (10, 14, 16). The denominator, a measure of total days for which PDC is computed, was the total number of days between first and the last

prescription refill. The numerator was the sum of the drug supply days, excluding the day supply of the last refill. The ratio of the numerator and denominator, represented the proportion of days which were covered by a drug (i.e. drug available for use or was in possession) during the study period. The PDC doesn't address excess supply due to overlap of day supply from early refills (where a refill occurred prior to exhaustion of day supply from previous refill). It simply measures the availability of the drug for each day of the study period. The PDC was computed separately for two broad classes of diabetes medications: oral (coded in the pharmacy files as VHA drug class HS502) and insulin (HS501). PDC values for those veterans who were put on insulin during the study follow-up were computed by taking an average of the oral and insulin PDCs. The PDC was calculated as a continuous measure with values ranging from 0 to 1.00 (or 0-100%), depending proportion of days covered. Two categorical variables, derived from the continuous measure, were used in the analyses. A 4-level categorical variable for PDC was used for descriptive purposes, where the PDC was divided into: poor (<0.6), moderate (0.6-<0.8), good (0.8-<0.9), and excellent (=> 0.9). The primary outcome variable for medication adherence that was used in all our analyses was a dichotomized PDC variable: adherent (PDC =>0.8) and not-adherent (<0.8). The 0.8 or 80% is a commonly used cut-off in pharmaco-epidemiological literature (15, 10). Sensitivity analyses were done by repeating the analyses at different cut-off levels, 0.7 and 0.9.

Persistence was calculated as the time from the initiation of diabetes treatment to the first discontinuation (or treatment gap) in diabetes treatment during the first 2 years following treatment initiation (15, 7, 17). Diabetes treatment was considered to be discontinued,

when the refill gap exceeded a "grace period" of 60 days from the exhaustion of previous refill's day supply (15, 7, 17). Patients who experienced a treatment gap during the first 2 years were marked as non-persistent and their follow-up ended on the date till which the day supply of the last refill would have lasted. Follow-up for patients with no treatment gaps continued till censorship (date of death, lost to follow-up, or end of two year period, whichever came first). We analyzed persistence with any diabetes medication rather than for specific medications. If during the first 2 years, veterans switched from index drug class to another mono oral agent or were intensified to dual oral agents or insulin, all the diabetes medications were treated as exchangeable when computing persistence.

Exposure variable

The number of CCIG groups or categorization used for the medication adherence study was different from those used for medication persistence study. The exposure variable in the adherence study was the same variable with 9 CCIG_CCIG groups used in the HbA1c trends study. The 9 CCIG_CCIG groups were: none_none (when both baseline and final CCIG were none), none_other (when baseline CCIG was none and the final CCIG was either concordant, discordant, both, or dominant), concordant-concordant, concordant_other, discordant_discordant, discordant_other, both_both, both_other, and dominant. This variable accounts for baseline and subsequent change in comorbidity status during study follow-up. Both the HbA1c trends study and the adherence study used data till end of FY2010 and have extended follow-up periods (Chapter 3).

Unlike in the adherence study, the primary exposure variable for the persistence study was a 5-level CCIG variable based on the type of comorbid illnesses present at baseline (or diabetes treatment initiation). The 5 CCIGs were: none, concordant only, discordant only, both, and dominant. The persistence study had shorter follow-up interval (first two years following treatment initiation) and fewer incident illnesses, which were captured using a 5-level incident CCIG variable (none, concordant, discordant, both, and dominant; all prefixed with term "incident"). Here the variable value "incident none" indicated no onset of new illnesses, while other values represented the type of comorbid illnesses that were incident in the first 2 years following treatment initiation.

Covariates

The following covariates: age groups, race/ethnicity, gender, marital status, VHA priority code, and baseline BMI categories were common to both adherence and persistence analyses (Previously described in chapter 3, page 50).

Specific to the adherence analyses the following variables were included: i) change in BMI (last observed BMI- baseline BMI), ii) average annual measures for non diabetes-related face-to-face visits, iii) diabetes-related face-to-face visits, iv) number of non diabetes medications, and v) an indicator variable for insulin initiation. The average annual measures were obtained by rounding sum total of visits/medications accrued during study follow-up by study duration in years.

For the persistence analyses the baseline covariates recorded at the time of diabetes treatment initiation were used.

Statistical Analyses

The characteristics of the study cohort have been described in detail in previous chapter (please refer to chapter 3, page 54). We used frequencies and proportions (for categorical data) and means and medians (for continuous data) to describe the study outcomes and their relative distributions across the comorbidity groups.

For adherence analyses, we ran regression models to compute the odds for being adherent to diabetes medications ((PDC =>0.8) and their association with comorbidity groups. We first fit unadjusted logistic regression models with just CCIG_CCIG variable. The multivariable logistic regression model accounted for age, race/ethnicity, gender, marital status, VHA priority code, average annual non-diabetes related and diabetes-related fact-to-face visits, non-diabetes medication classes, baseline BMI, change in BMI, average HbA1c, and initiation of insulin during study period. All the above mentioned covariates were independently significantly associated with medication adherence and were also part of the final model. The corresponding AIC value for the fuller model with all covariates was the lowest indicating a good fit compared to the partially fit models. Sensitivity analyses included repeating the analyses using PDC =>0.7 and PDC=>0.9 cut-offs for medication adherence.

For persistence analyses, we examined time to first diabetes treatment gap (discontinuity of more than 60 days) from initiation of diabetes treatment with event of failure being non-persistence (having a treatment gap). We first fit a crude survival curve describing the pattern of persistence in the overall cohort for data till end of FY2010. Regression analyses included first fitting unadjusted Cox proportional hazards regression model with

only the baseline CCIG variable. We then fit a multivariable model that accounted for all baseline covariates. Gender and F2F visit frequency variables were not significantly associated and were dropped from the models. The final Cox proportional hazards model included the following variables: baseline and incident CCIGs, age, race/ethnicity, marital status, VHA priority code, baseline HbA1c, baseline BMI, and number of non-diabetes medication classes at baseline. This model also had the lowest AIC value compared to other models, indicating good fit. Using Schonfield residuals, the proportional hazards assumption was tested for baseline CCIG variable in the final model. The correlation between Schonfield residuals and the time to treatment gap was insignificant suggesting that proportional hazards assumption was not violated.

A two-sided alpha of 0.05 was used as level of significance for statistical tests. All analyses were done using SAS v.9.2 software. We used SAS PROC LOGISTIC procedure step to run the logistic regression models. Cox proportional hazards regression models were fit using PROC PHREG procedure step.

4.3 Results

The study cohort has been described in the previous chapter (please refer to chapter 3, page 54)

Only half of the study veterans (49.42%) were adherent to their diabetes medications (adherence defined as => 0.8 PDC). The highest and lowest levels of adherence were seen in the concordant_concordant (55.54%) and none_other CCIGs (46.98%), respectively. Table 4.1 presents the distribution of the PDC categories across the

CCIG_CCIGs. Table 4.2 presents the logistic regression results modeling for adherence. The findings from the unadjusted model show that having concordant illnesses was associated with increased odds for adherence to diabetes medications compared to having no additional illness [concordant_concordant CCIG- 1.18(1.09-1.27 and both_both CCIG 1.12 (1.05-1.20)]. The odds of adherence to diabetes medications among veterans with discordant and dominant illnesses were significantly lower by 10-15%. In the adjusted analyses accounting for covariates, all CCIGs had reduced odds for diabetes medication adherence, compared to the none_none CCIG. These odds were significantly lower in the discordant, both, and dominant CCIGs. In the dominant group the odds were lower by 22%. Lower odds for adherence were seen among veterans with discordant illnesses, discordant_discordant (0.88 (0.82-0.94)) and discordant_other (0.77 (0.72-0.82)). The odds for adherence were lower even in concordant_concodant CCIG (0.92 (0.85-1.00)), however the results were not statistically significant. Increasing age was correlated with increase in adherence levels. Compared to veterans aged 55 years or less, the odds for being adherent were higher by 26% to 35% in the older age groups. Being female was associated with lower odds for being adherent (0.82 (0.75-0.90)). All race/ethnicity groups had lower adherence rates compared to Whites. African-Americans (or Blacks) had almost 50% lower odds for being adherent with their diabetes medications. Other factors associated with lower odds for adherence were: being unmarried, making more non-diabetes related face-to-face visits; initiating insulin during the study; while obese compared to normal weight was associated with increased adherence (Table 4.3). Frequency of diabetes-related face-to-face visits was positively associated with adherence to diabetes medications. Compared to veterans who made 2 or fewer diabetes-related

face-to-face visits per year on average, among those who made between 3-4 visits and 4 or more visits, the odds for adherence increased by 25% and 38%, respectively. Diabetes medication adherence, assessed using pharmacy refill data, was strongly associated with number of non-diabetes medications concurrently taken by the veteran. Compared to those with 4 or fewer medication classes, the odd ratio for being adherent was 1.35 (1.30-1.41) among those with number of non-diabetes medication classes between 5 and 8. The odds for adherence increase further among those with 9 to 12, and more than 12 medication classes by 74% and 211%, respectively.

Results from sensitivity analyses using PDC data computed from only oral diabetes medications were similar those using average PDC of oral and insulin PDCs, which were computed separately (Table 4.6). We chose to present results from our primary analyses, which used the average PDC values. Changing the cut-off for defining adherence as PDC => 0.7 and => 0.9 didn't affect the direction or magnitude of most of the associations indicating our study findings are robust (Tables 4.4 and 4.5).

In the first 2 years following diabetes treatment initiation, non-persistence rates were lower among veterans with concordant illnesses (concordant 56.35% and both 55.10%). Higher rates for non-persistence with diabetes medications were seen in veterans with dominant illnesses (60.07%) and no comorbidities (59.72%). In the overall cohort, the mean time to first diabetes treatment gap was 14.52 (8.86) months. The interval was shorter amongst those with no comorbid illnesses or those with dominant illnesses (Table 4.7)

Table 4.8 presents results from the Cox proportional hazards regression models, modeling for non-persistence with diabetes medications. In the unadjusted model, except for having dominant illness, all other type of comorbid illnesses were associated with lower odds for non-persistence (Table 4.8). The hazards ratio (HR) (95% CI) for dominant CCIG was 1.06 (1.01-1.10).

The final adjusted model accounted for the following covariates; age, race/ethnicity, marital status, priority code, concurrent number of non-diabetes medication classes, baseline BMI, and baseline HbA1c. After adjusting for the covariates, we found no relationship between baseline CCIGs and non-persistence, except for dominant CCIG. Belonging to dominant CCIG at baseline increased the odds for non-persistence with diabetes medication in the first two years following treatment initiation by 12% (HR (95% CI) 1.12 (1.08-1.17)). Compared to having no incident illnesses, the incidence of dominant illness was associated with higher odds for non-persistence (HR (95% CI) 1.13 (1.09-1.18)). The unadjusted and adjusted survival curves are presented in Figure 4.2 and 4.3, respectively.

The odds for non-persistence increased from being 14% lower (for 55-64 years) to 8% lower (for over 75 years) compared to those less than 55 years of age. Being African-American (or Black) increased the risk for non-persistence compared to being White by 34%. Factors that were associated with lower odds for non-persistence were: being married, having higher BMI levels, having baseline HbA1c => 9%; while the following factors were associated with higher odds for non-persistence: being disabled, have low income priority status, having baseline HbA1c value <7% (Table 4.9). Persistence with

diabetes medications was likely to be higher when veterans were taking more concurrent non-diabetes medications. The hazards ratio for becoming non-persistent was 0.87 (0.85-0.89) among those with 5 to 8 non-diabetes medication classes, compared to those with 4 or fewer. The odds for non-persistence decreased further in those with 9 to 12, and more than 12 non-diabetes medication classes by 19% and 24%, respectively (Table 4.9).

4.4 Discussion

The diabetes medication adherence rate in our study cohort was close to 50% (PDC => 0.8). Almost all comorbidity groups were associated with lower rates of medication adherence, indicating that the presence of any comorbidity adds challenges to being compliant with diabetes medications. As hypothesized, compared to veterans with no comorbidities, veterans belonging to dominant and discordant CCIGs (discordant_discordant & discordant_other) had significantly lower odds for adherence. Veterans with only concordant illnesses did not have significantly lower adherence rates. The behavior of veterans belonging to various comorbidity groups vis-à-vis diabetes medication adherence was as conceptualized in the Piette and Kerr theoretical framework (18, 19).

With regards to persistence, at end of two years following diabetes treatment initiation about 60% of veterans were non-persistent with their diabetes medications regimens. Rates of non-persistence were comparable across baseline comorbidity groups. Regression analyses showed that only those veterans with dominant illnesses were significantly less likely to be persistent with diabetes medications, compared to those with no comorbidities.

Our study results were comparable with other studies that examined adherence to diabetes medications. In a similar analysis, employing medication possession ratio (MPR) as the adherence measure, using national cohort of veterans with both incident and prevalent diabetes Egede et al reported an MPR close to 0.80 (9). Compared to PDC, MPR is known to overestimate medication adherence (14, 20, 21). Other studies, including a meta-analysis, reported that the proportion of diabetes patients who were adherent to their diabetes treatment regimens ranged between 36-93% (1, 22). The wide variation in the adherence rates across these studies is due to differences in study settings, health care systems, diabetes duration, geographical variations, patient populations, adherence metrics and definitions. Similar to other studies we found being White and older was associated with higher adherence levels and being a female veteran was associated with lower adherence rates than male veterans (9). Other factors which were associated with higher adherence rates were higher diabetes-related face-to-face visits, number of non-diabetes related medications, baseline BMI levels; lower rates for adherence were seen among veterans with no social support (not married) (9) and made more non-diabetes related face-to-face visits.

Yeaw et al reported that at end the first year following treatment initiation with anti-diabetes medications, 46% were non-persistent, using 60-day refill grace period, similar to our study (7). Being young decreased risk for non-persistence, contrary to other studies where older patients were found to be more persistent. Gender was not a predictor for persistence in our analyses. Decreased risk for non-persistence was seen amongst

White veterans, veterans with higher BMI levels and higher number of non-diabetes medications.

Some of the strengths of our study was the use of large, national-level, population based database with extensive clinical data to test our research hypothesis. We included an extensive list of comorbid illnesses in our analyses to study how they were related with diabetes treatment adherence and persistence, which was possible due to high prevalence of comorbidity among veterans. The veterans face limited barriers to accessing clinical services and pharmacy benefits at the VHA, which acts as the primary source for medical care for most veterans and thereby making our study findings more reliable with almost complete data for our study variables. Additionally, the findings are less confounded by economic burden and costs barrier to filling prescribed medications, which is an often cited reason for medication non-compliance (23). We accounted for an extensive list of covariates in our analyses. We assessed adherence over a prolonged period of follow-up (24).

One of the study limitations was the limited generalizability of our study results to the broader US population, as the VA population is predominantly male, older, and sicker than the general population. We did not study adherence and persistence patterns vis-à-vis individual diabetes medications. We used pharmacy refill databases to assess adherence, which doesn't necessarily correlate with the patient actually consuming the medication and thereby possibly overestimating the true adherence. Prior studies have shown that these indirect measures correlate well with more direct approaches to

measuring adherences, such as, pill counts, direct observation of medication taking, electronic monitoring, and measuring drug or metabolite levels (10-13). Some of reasons associated with poor medication compliance, such as patient's motivation, education level, diabetes self-management skills, social support, and quality of the interaction with their physicians, and others are not available in our databases to account for (25, 26). Our analyses didn't include medical data originating from medical care/services received from non-VHA sources, such as, Medicare or private insurance for certain health care services. One potential source for bias in our adherence analyses could come from informative censoring arising from variations in mortality rates across the various comorbidity groups and possible linkage between lower adherence to diabetes medications and survival. We might have over-estimated adherence in groups with higher mortality.

Several studies have shown that adherence and persistence with diabetes medications is linked to lower HbA1c levels, lower complications, and costs (2, 3, 5, 6). Realizing the importance of improving adherence and persistence to realize optimal health care quality, they have been introduced as quality measures by the National Quality Forum (7, 8). Specific areas for intervention need to be identified and evidence based programs aimed at improving medication adherence and persistence are needed. These programs must be tailored based on the comorbidity profile of the patients. Enhancing motivation levels among patients through diabetes education and training programs intended to improve their diabetes self-management skills; re-training physicians on patient communication skills, risk-factor management; integrating care delivery through more care coordination

are a few interventions that might help address the huge challenge of improving patients' medication adherence and persistence levels.

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Chapter V: Type of chronic comorbidity and diabetes treatment intensification

5.1 Background

Several studies have shown that elevated HbA1c levels, beyond target levels, increase morbidity and mortality risk in diabetes patients (1-7). In the previous chapter we explored one of the key barriers to achieving optimal glucose control, the lack of adequate medication adherence and persistence, which were patient-centered behaviors. Clinical inertia or lack of treatment intensification is another known barrier to successful management of glucose levels (8-9). This construct is more physician-centered, and occurs when a health care provider doesn't initiate or intensify diabetes medication regimens in spite of evidence of poor or worsening glycemic control (9). Despite well-established evidence-based guidelines recommending timely intervention in face of poor or worsening glycemic control, clinical inaction is fairly common (10-13). Studying the magnitude and reasons for failure to intensify diabetes medication regimens in timely manner will help in developing appropriate policy prescriptions that will enable patients, physicians, health care systems, and society at large in realizing the gains from optimal diabetes management. Previous studies on clinical inertia or lack of treatment intensification have focused on themes such as physicians' and patients' attitudes, trust, abilities, preferences, patient medication adherence, and barriers to care (14-24).

Very few studies have looked at how presence of multiple comorbid illnesses influences physicians' decision-making while managing elevated glucose levels in diabetes patients.

The primary purpose of this study was to examine the relationship between type of chronic comorbidity and diabetes treatment intensification in the first year following index treatment failure. We hypothesized that, compared to having no additional comorbidities than diabetes (none CCIG), having concordant illnesses would be associated with higher odds for treatment intensification, among veterans with discordant illnesses these odds would be lower, and the presence of dominant illnesses will reduce the odds even further.

5.2 Methods

Data Source / Study Design / Study Cohorts

We used a retrospective cohort study design. The study cohort comprised of 28,472 veterans, who were part of the 79,249 veterans that initiated anti-diabetic medication therapy, using a mono oral agent, between FY2000-02 (Figure 1.1 and 1.2). The index event for induction into this study cohort was failure of index diabetes treatment, defined as having an elevated HbA1c (>8%) at least 3 months following diabetes treatment initiation, while they were still on the index diabetes medication class. The date of the first HbA1c test result >8% was used as the index date or baseline. The study follow-up extended for one year (365 days from the index date) and assessed the proportion of veterans whose diabetes treatment was intensified in that period.

Outcome variables

Diabetes treatment intensification was the outcome measure. We defined intensification as either addition of second oral agent (to the current index mono oral agent) from a

different oral diabetes medication class than the index class, and/or initiation of insulin. Intensification received (yes vs. no) was analyzed as a binomial measure.

Exposure variable

Our primary exposure variable was a 5-level categorical variable based on the presence of comorbid illnesses at study baseline. We categorized close to 60 chronic comorbid illnesses into 5 chronic comorbid illness groups (CCIGs): none (with no comorbidity), concordant only, discordant only, both concordant and discordant, and dominant. The CCIG classification was based on the type of comorbidities and the degree to which their disease management overlaps with that of diabetes. ICD-9-CM codes from inpatient and outpatient files were used to identify presence of comorbidities. Ascertainment of comorbid illness' presence and CCIG assignment, was done primarily at baseline using clinical data from the corresponding prior 3 years (1 baseline year and 2 look-back years), defined by presence of 2 or more codes. A second variable for comorbidities captured incident illnesses during the study follow-up. We employed similar criteria of requiring 2 or more codes during the study follow-up year with no codes in prior two look-back years to identify incident illnesses. This variable took similar values as primary exposure variable with none representing no additional incident illnesses during study follow-up and was adjusted for as a covariate to account for impact of incident illnesses on treatment intensification.

Covariates

The following covariates were used in this study, all of which were categorical-age groups (<55, 55-64, 65-74, 75 or more), race/ethnicity (White, African-American (or Black), Other), gender (male, female), marital status (married, not married), VHA priority code (co-pay, low-income, moderately disabled, severely disabled), non-diabetes-related face-to-face visits (<= 4, 5-8, 9-12, > 12), diabetes-related face-to-face visits(<= 2, 3-4, > 4), number of non-diabetes medication classes(<= 4, 5-8, 9-12, > 12), proportion of days covered (PDC) (<0.7, 0.7-0.8,0.8-0.9, >0.9), body mass index (BMI) (<25, 25 to <30, 30 to <35, => 35), and baseline HbA1c categories(< 7%, 7 to < 8%, 8 to <9%, 9% or more). These covariates were described previously (Chapter 3).

Specific to the intensification analyses, we had two additional covariates: HbA1c at index failure and time to index treatment failure. HbA1c at index failure was categorical measure with 3 levels (8 to <9%, 9 to <10%, 10% or higher). Time to index treatment failure indicated the length of duration between diabetes treatment initiation and index treatment failure and was also used as a categorical measure. It had 4 categories (< 1 year, 1 to <2 years, 2 to <3 years, 3 or more years).

Statistical Analyses

Proportions were used to describe the baseline characteristics of the study cohort and their relative distributions across the comorbidity groups. Cross-tabs were used to display the distribution of the unadjusted proportions for the study outcome by comorbidity groups. Binomial logistic regression models were used for the regression analyses. We first fit the unadjusted model with only the CCIG variable in the model. Then we fit a

fully adjusted model with all covariates. Covariates that were not statistically significant were excluded from the models till all covariates were found to be significantly associated with the outcome. We compared goodness-of-fit of fuller model with the partial models using AIC values and our final model was found to have lowest AIC values. Gender, incident CCIG, and non diabetes-related visits variables were dropped from final model as they were not significant. The final adjusted multivariable logistic regression model included the following covariates: age groups, race/ethnicity, diabetes-related face-to-face visits, PDC, number of non-diabetes medication classes, baseline BMI, HbA1c at index failure, and time to index treatment failure, in addition to CCIGs. We tested for interaction between CCIG variable and age groups, PDC, BMI, HbA1c at index failure, and time to index treatment failure. None of these interactions were statistically significant and so we did not conduct any stratified analyses and used only the main effect terms in the model. A two-sided alpha of 0.05 was used as level of significance for statistical tests. All analyses were done using SAS v.9.2 software. We used SAS PROC LOGISTIC procedure step to run the logistic regression models. To assess the impact of attrition due to death on our study results, we did a sensitivity analyses by repeating the analyses in a subset of veterans who survived beyond the first year following index treatment failure. To see if intensification patterns depended on how treatment failure was defined, we performed sensitivity analyses by repeating the analyses using different HbA1c levels for defining index treatment failure, >7% and > 9%.

5.3 Results

Out of the 28,472 veterans who failed index diabetes treatment, close to 30% were free of comorbid illnesses. Patients with concordant illnesses constituted ~12% of the study cohort; 29.57% had discordant illnesses and 17.53% had both concordant and discordant illnesses. About 10% of patients were diagnosed as having a dominant illness at baseline (Table 5.1). The proportion of study veterans with incident illnesses during the one year study period was about 10% in the overall cohort.

Diabetes patients with either no comorbidities or those with discordant illnesses were more likely to be younger, female, and non-white (Table 5.1). The concordant group tended to be older (22.02% over 75 years), had the highest levels of being married (61.21%), low-income veterans (47.23%) and veterans with co-pay (22.44%). The discordant group had the lowest levels in all these categories (53.13%; 36.82%; 11.28%). A service-connected disability, as measured by the VHA priority code, was more prevalent among patients with discordant and dominant illnesses. Non-diabetes related F2F visits were disproportionately higher in groups with discordant only, both discordant and concordant, and dominant illnesses, as were the number of non-diabetes medication classes, while the number of diabetes related F2F visits were comparable across the CCIGs. Adherence levels were higher in concordant CCIG compared to other groups where close to 35% had PDC values of 0.9 or higher. Obesity was slightly less prevalent among veterans belonging to concordant (~53%) and dominant (43.53%) illness groups, compared to close to 60% prevalence in other groups. The proportion of veterans who failed index treatment within 12 months of diabetes treatment initiation decreased from 42.48% (none CCIG) to 17.48% for those belonging to dominant CCIG. Higher

proportion of veterans with index treatment failure HbA1c > 10% were seen in none (21.85%) and discordant (20.23%) CCIGs compared to the overall cohort (18.94%).

Table 5.2 shows that within the first year following index treatment failure, out of 28, 472 veterans 43.09% were intensified to either dual therapy or insulin. Intensification rates were higher for veterans with discordant (47.59%) and both concordant and discordant illnesses (45.17%). Among those who were intensified, close to 96% were intensified to dual oral therapy. This proportion ranged between 91% for dominant CCIG to 97% for none CCIG.

Table 5.3 presents results from the unadjusted and adjusted logistic regression models for treatment intensification. The findings from the unadjusted model show that having a discordant illness or having both discordant and concordant illnesses was associated with significantly increased odds (odds ratio (OR) (95% CI)) for diabetes treatment intensification [discordant CCIG: 1.35 (1.27-1.45) and both CCIG:1.24 (1.14-1.33)]. However, after covariate adjustment, the odds for intensification were no longer significantly higher in the two groups [discordant CCIG: 1.06 (0.99-1.14) and both CCIG: 0.99 (0.91-1.08)]. Amongst veterans with concordant (0.90 (0.82-0.99)) and dominant (0.90 (0.82-0.99)) these odds were lower by 10%.

The detailed results from the final adjusted model for treatment intensification are presented in Table 5.4 Age was associated with intensification. Compared to younger veterans (aged < 55 years), the odds for intensification decreased as age increased, from 8% below unity to 27%, and 51% in the 55-64, 65-74, and 75 and older age groups,

respectively. African-Americans (or Blacks) were significantly less likely to be intensified compared to Whites (0.76 (0.70-0.81)). More number of diabetes-related face-to-face visits was related with higher odds for intensification. Compared to those with high adherence (PDC >0.9), those with PDC <0.7 had lower odds for dual intensification (0.80(0.75-0.86)). Veterans with more than 4 concurrent non-diabetes medication classes were 27-38% more likely to be intensified, compared to those with 4 or fewer medications. Higher HbA1c levels at index treatment failure were associated with increased odds for intensification. Compared to failure HbA1c between 8-9%, the odds for intensification among those with failure HbA1c between 9-10% were 45% higher, and even higher for those with failure HbA1c > 10% (1.89 (1.76-2.02)). The greater the length of time between treatment initiation and index treatment failure, the greater were the odds for being intensified. The odds increased by 20% if the interval was between 2-3 years, by about 70% if the interval was more than 3 years, compared to those who experienced index treatment failure within one year of treatment initiation. Finally, obesity was associated with increased odds for intensification compared to being non-obese. (Table 5.4)

The results for treatment intensification were similar when the analyses was limited to those who survived the first year following index treatment failure (n=23,172), and when index treatment failure definition was changed to >7% (n=44,539) or >9% (n=13,516) (Tables 5.5-5.7).

5.4 Discussion

Our study showed that during the first year following index diabetes treatment failure among those on a mono oral agent, only 43% of the 28,472 study veterans received treatment intensification (i.e. addition of second oral agent (or dual therapy) or initiation of insulin). Almost all intensifications (~95%) were addition of a second oral agent. Type of comorbidity was not significantly related to treatment intensification. However, those with concordant or dominant illnesses were less likely to be intensified compared to those with no additional illnesses. Incident comorbidity did not impact treatment intensification.

Several studies have shown that lower HbA1c levels are associated with lowered diabetes complications and mortality rates (1-7, 25-26). The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) treatment algorithm recommends regular monitoring of HbA1c values and intensification to dual therapy or basal insulin following treatment failure with initial mono oral agent (25). Despite these guidelines, several other studies, including this one found the existence of clinical inertia or lack of treatment intensification when there was sub-optimal glycemic control (8, 10, 11, 12). Immediate intensification following an elevated HbA1c >8% can benefit the patients by slowing progression of diabetes, reducing lifetime cumulative hyperglycemic load, and thereby preventing, postponing or reducing severity of the complications (25-27). The fact that close to 60% of the study cohort with indications for treatment intensification were not intensified during the first year highlights the several missed opportunities for improving glycemic management. In a study of patients belonging to a private managed care organization who failed index diabetes treatment

Grant et al reported that at the end of first year only 33.3% received treatments intensification (28). In another study using the GE database, Fu et al reported that only 64% of patients who failed metformin mono therapy were intensified during the study period with a median time to intensification of 14 months (12).

Similar to other studies, our results have shown a positive association between treatment intensification and younger age groups (12), medication adherence (28), higher levels of treatment failure HbA1c (11, 12, 29), White race (28), higher BMI levels (12), and higher diabetes-related visits (11, 12). We additionally found a positive association between number of concurrent medications and odds for treatment intensification.

The study results did not directly support the theoretical concepts of the Piette and Kerr framework (30, 31). We hypothesized that patients with concordant illnesses would have a higher likelihood of treatment intensification, and that the discordant and dominant groups would have a lower likelihood. The results showed that having dominant illnesses was associated with lower odds for intensification as hypothesized. However, those with concordant illness also had a lower likelihood. The possible reasons for why concordant illnesses presence was seen to lower the odds for intensification could be: 1) many of them might have received dose increases, which we were unable to capture in our data, 2) given the failure HbA1c levels were lower in this group, they probably achieved glycemic control with dose titration itself without need for additional or new medications, 3) side-effects profile of the candidate agents for medication intensification were associated with relatively higher morbidity risk in this group than others, 4) being the

most adherent group of all CCIGs physicians probably focused more on patient counseling and motivation for life-style modifications to achieve optimal glycemic control, and 5) concordant CCIG comprised of veterans who were relatively older than those from other CCIGs and physicians probably didn't weigh the risk-benefits favorably towards intensification given their age. One can hypothesize the same factors playing a role, albeit in a contrary manner, resulting in discordant illnesses being associated with similar odds for intensification rather than lower odds compared to none CCIG.

Some of the strengths of our study was the use of large, national-level, population based database with extensive clinical data to test our research hypothesis. We included an extensive list of comorbid illnesses in our analyses to study how they were related with treatment intensification, which was possible due to high prevalence of comorbidity among veterans. The veterans face limited barriers to accessing clinical services and pharmacy benefits at the VHA, which acts as the primary source for medical care for many veterans and thereby making our study findings more reliable with almost complete data for our study variables. We accounted for an extensive list of covariates in our analyses.

One of the study limitations was the limited generalizability of our study results to the broader US population, as the VHA population is predominantly male, older, and sicker than the general population. We did not use dose increases for the index drug as an intensification measure as we did not have data on the detailed dose instructions to capture dose changes. We did not focus on individual medications but only examined

addition or initiation of new class of drugs. As with most administrative databases, the VHA databases lack granularity or detailed information from clinical encounters that could provide a context for interpretation of our study findings. For example, the VHA administrative databases are deficient on key patient-level (self-care efficiency, motivation, social support, interaction with physician, and others) and physician-level (workload, competence, communication skills, and others) characteristics that might better explain our study outcomes. Studies have shown several of these physicians' and patients' related factors influence treatment intensification (14-24, 32). These limitations are common to administrative data based analyses and are not unique to our study. Our analyses didn't include medical data originating from medical care/services received from non-VHA sources, such as, Medicare or private insurance for certain health care services. Our outcome assessment was specific to only treatment intensifications in an index treatment failure cohort. However, in individual scenarios with patients who are old; sick; frail; who experienced or are at risk for experiencing side-effects from anti-diabetes medications, including hypoglycemia, the correct action by the clinician was probably non-intensification of treatment (33). We characterized all clinical inactions, including appropriate ones, as non-intensifications. A qualitative study that examines a series of clinical encounters, interviews patients and physicians on their willingness, preparedness and attitudes towards adequate glycemic control will provide reasons for why treatment intensification occurred or did not occur and the choice of treatment modality for intensification.

In summary, more than 50% of veterans who fail index diabetes treatment do not get intensified in the first year following failure. Treatment intensification, when it occurs, is predominantly intensification to dual. Presence of concordant or dominant comorbid illnesses was associated with lower odds for treatment intensification.

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Chapter VI: Conclusion

6.1 Conclusion

Presence of comorbidities complicates diabetes management for patients, providers, and health care systems depending on the amount additional resources available for successful management of both diabetes and the comorbidities (1-5). In the face of increasing burden of comorbidity with an aging U.S. population, unless adequately staffed and resourced health care systems can be overwhelmed by the magnitude of health maintenance activities (screening, testing, counseling, and treatment) that need to be performed to ensure delivery of quality care to their patients (1-5).

Piette and Kerr framework proposed a novel taxonomy for classifying comorbidities based on how they might impact diabetes care (6). This classification was based on "competing demands "framework (7), as per which, illnesses with similar risk factor profiles and management plans as that for diabetes management (concordant), would compete less for limited health care resources compared to more un-related illnesses (discordant and dominant). The framework hypothesized that having concordant set of illnesses in addition to diabetes would be associated with similar or better quality of diabetes-related care, compared to having no additional illnesses. On the other hand, when patients are burdened with discordant comorbidities in addition to diabetes their diabetes care might be compromised. For those with dominant illnesses, health care needs of dominant illnesses might overwhelm care priorities and result in even worse diabetes care. We applied this framework using an extensive list of about 60 chronic comorbid illnesses and classified study veterans into 5 chronic comorbid illness groups: none (with

no additional illnesses other than diabetes), concordant only, discordant only, both concordant and discordant, and dominant and examined the relationship between comorbidity groups and various aspects of diabetes care in a large managed care setting like the Veterans Health Administration (VHA) using national-level population-based data.

We first evaluated the Piette and Kerr framework using as study outcomes: 3 process measures (HbA1c testing, and LDL-C testing, and diabetes-related face-to-face visits) and 2 treatment goal measures (meeting goals of HbA1c < 8% and LDL-C < 130 mg/dL) in a cohort of 42,826 veterans with new-onset diabetes (8). We found empirical support for the framework's hypothesis. Examining the relationship between longitudinal HbA1c trends and comorbidity groups was our second analyses. For this analysis, we followed a cohort of 79,249 veterans who initiated anti-diabetic treatment in FY2000-02 and were followed for a maximum of 11 years. We further examined impact of comorbidity on patients' and physicians' behavior. To understand how comorbidities impacted patient behavior we studied the adherence to diabetes medications (adherent defined as => 0.8 proportion of days covered (PDC)) and non-persistence (first treatment gap > 60 days) patterns by comorbidity groups. The adherence and persistence studies used the anti-diabetic treatment initiation cohort that was used in HbA1c trends study. To evaluate how physicians responded in presence of comorbidities, we evaluated whether presence of comorbidities impacted physicians' behavior vis-à-vis diabetes treatment intensification when indicated. We studied treatment intensification in an index treatment failure cohort comprised of 28,479 veterans who failed index treatment with an HbA1c >

8% at least 3 months following treatment initiation (Figure 1.1 and 1.2).

The pattern of association between the comorbidity groups and the various diabetes-related care measures was not uniform across the studies and differed by the outcome measure. In all studies we found that the utilization frequency was much higher among veterans with discordant and dominant illnesses, compared to none and concordant illnesses. This was not surprising as the burden of illness seems to dictate the amount of utilization and also with limited barriers to access the VHA system appears to be able to accommodate this increase in utilization.

The highlights of the findings by the comorbidity groups, compared to those without comorbidities, were:

Presence of concordant illnesses was associated with similar odds for meeting most of the process and treatment measures, except for meeting treatment goal of LDL-C <130 mg/dL (higher odds), regardless of visit frequency. Veterans belonging to concordant CCIG were initiated at lower HbA1c levels, achieved comparable HbA1c levels at end of 6 months, rose at slower pace than none CCIG, and end up at lower levels at end of study period. Adherence and non-persistence rates were similar to those with no additional illnesses. Treatment intensification odds were lower among veterans with concordant illnesses. HbA1c levels (flatter trajectories/slower rate of rise following initial drop and lower HbA1v values at end of the study) were correlated with care process (higher adherence) in the concordant CCIGs.

Presence of discordant illnesses was associated with lower odds for meeting both process and treatment measures at lower end of visit frequency spectrum but were comparable to those without comorbidities when visit frequency approached 12 visits or more. Veterans belonging to discordant CCIGs were initiated at higher HbA1c levels, achieved comparable HbA1c levels at end of 6 months, rose at faster pace and had higher HbA1c levels at the end of the study period. In veterans with discordant illnesses, non-persistence and treatment intensification odds were similar to those without additional illnesses. However, adherence rates were significantly lower among veterans with discordant illnesses. HbA1c levels (steeper trajectories/rapid rise in HbA1c levels following initial drop) were correlated with care process (lower adherence) in the discordant CCIGs.

Presence of dominant illnesses was associated with significantly lower odds for meeting both process and treatment measures regardless of visit frequency. Veterans belonging to dominant CCIGs were initiated at intermediate HbA1c levels, achieved comparable HbA1c levels at end of 6 months, rose at significantly slower pace than none CCIG, and end up at significantly lower levels at end of the study period. Presence of dominant illness was associated with lowered adherence, persistence, and treatment intensification odds compared to absence of comorbidities. HbA1c levels (flat trajectory/slow rise in HbA1c levels following initial drop) were not correlated with care process (lower adherence, persistence, and intensification) in the dominant CCIGs.

In summary, we found mixed findings with weak support for the Piette and Kerr framework for concordant and discordant CCIGs. With dominant illnesses, HbA1c levels were lower despite lower adherence and treatment intensification. There are various reasons that could account for the mixed findings. One key reason could be attributed to the study setting. The VHA provides high quality care for veterans with limited barriers (be it financial or otherwise) and was found to be adequately compensating to needs for excess care in certain illness groups, such as, discordant and dominant illnesses. Moreover, with digitalized health care systems the VHA is better integrated and more organized to deliver coordinated care. Previous studies have shown that quality of care at VHA is better than other health care systems (9-11). We believe that replication of these studies in health care settings with more access barriers, less integration, and more resource constraints than the VHA may result in findings that are more supportive of the Piette and Kerr framework.

Achieving and maintaining glycemic control is the main stay of diabetes management. Chronically elevated glucose levels are known to be associated with increased mortality and morbidity (12-14). Following the results from landmark trials such as the UKPDS, an aggressive target of HbA1c < 7% was advocated for in all diabetes patients (12-18). However, later studies have highlighted the risks associated with aggressive glycemic control, particularly those associated with hypoglycemic complications (19, 20). Though the need to move away from "one size fits all" approach to setting treatment and process goals is well acknowledged, diabetes treatment guidelines still lack the clarity on how care providers should optimize treatment goals based on life expectancy, quality-of-life,

and comorbidity (21-23). In our studies we found that veterans with dominant illnesses were likely to have lower HbA1c levels, probably due their comorbidity, might not benefit from tight glucose control. In fact the American Geriatric Society has recently come out with recommendation for not intensifying anti-diabetic treatment regimens for patients with HbA1c above 7.5%, especially among older patients (65 or older) (24). On the other hand, we found younger veterans with discordant and no comorbidities, who failed to maintain lower HbA1c levels initially achieved following treatment initiation, could benefit from better glycemic management and assistance with improving diabetes medication adherence.

HbA1c levels for veterans with dominant illnesses were lower despite lower adherence and treatment intensification rates, indicating that HbA1c values are not directly driven by quality of diabetes care. The findings support the position that assessing quality of diabetes care based on HbA1c levels alone may not be a reliable, particularly among those with dominant illnesses. Our findings also suggest the need for developing novel patient safety measures to prevent overtreatment and to ensure that hypoglycemia is not a problem for these patient groups.

Shared decision making (SDM) is being increasingly seen as an ideal model for provider-patient interaction for making treatment decisions (25, 27). It is defined as an approach where clinicians and patients communicate together using the best available evidence when faced with the task of making decisions, where patients are supported to deliberate about the possible attributes and consequences of options, to arrive at informed

preferences in making a determination about the best action and which respects patient autonomy, where this is desired, ethical and legal. SDM role in improving patients' compliance with treatment and process measures is being widely recognized. The VHA-DOD guidelines are explicit in recommending shared decision making when setting treatment goals (27). The recently passed Affordable Care Act (ACA) has a provision for wider use of shared decision making (28). There is increasing need for studies similar to ours, which will help expand our understanding of the challenges to achieving desired glycemic control and the accompanying trade-offs between benefits and risks in the presence of comorbid illnesses. Evidence-based results generated from such studies will help improve the process of shared decision making and will also help supplement evidence from randomized controlled trials, which are limited in their generalizability due low comorbidity burden amongst their enrollees.

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Tables

Table 1.1 Data Sources*

Data Source	Data Fields	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
VHA	ICD-9-CM & CPT codes**	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Lab tests	NA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Lab results	NA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	Pharmacy (PBM)	NA	✓	✓	✓	✓	NU	NU	NU	NA	NA	NA	NA	NA
	Pharmacy (DSS)	NA	NA	NA	NA	NU	✓	✓	✓	✓	✓	✓	✓	✓
	Vitals File***	NA	NA	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
	DEpiC	NU	NU	NU	✓	✓	✓	✓						
MC	ICD-9 & CPT codes**	NU	NU	NU	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA
	Lab tests	NU	NU	NU	✓	✓	✓	✓	NA	NA	NA	NA	NA	NA
	Lab results													
	Pharmacy											NA	NA	NA

Abbreviations: VHA, Veterans Health Administration; MC, Medicare; ICD-9-CM, International Classification of Diseases, 9th Revision, Clinical Modification; CPT, Current Procedural Terminology; DSS, Decision Support Systems; PBM, Pharmacy Benefits Management Strategic Health Group; DEpiC, Diabetes Epidemiology Cohorts; NA, Not Available; NU, Not Used;

* VHA's fiscal years run from October 1st of prior year to September 20th of following year.

** From diagnoses and procedure codes from inpatient and outpatient care

*** File with data on height, weight, blood pressures, and mortality.

Table 2.1 Characteristics of veterans with incident diabetes in FY2003 (N=42,826)

			CCIGs			Overall
Characteristics*	**None (n=8,544) %**	**Concordant Only (n=5,612) %**	**Discordant Only (n=12,902) %**	**Both (n=10,772) %**	**Dominant (n=4,996) %**	**(n=42,826) %**
Age Categories						
Under 55 years	27.31	12.01	38.51	17.57	14.31	24.71
55-64 years	32.58	22.65	30.89	21.22	18.45	26.27
65-74 years	26.44	34.84	18.93	30.20	28.56	26.47
Over 75 years	13.67	30.51	11.66	31.01	38.67	22.55
Gender						
Male	95.66	98.33	94.82	97.73	97.02	96.44
Female	4.34	1.67	5.18	2.27	2.98	3.56
Race						
White	63.47	79.81	67.44	81.93	78.54	73.21
Black	14.17	11.33	18.11	12.18	15.13	14.60
Other	18.75	7.15	11.32	4.34	3.70	9.61
Hispanic	3.60	1.71	3.14	1.55	2.62	2.58
Marital status						
Married	62.06	66.66	56.06	64.61	61.97	61.49
Not married	37.37	32.88	43.50	35.06	37.75	38.09
Missing	0.57	0.46	0.44	0.32	0.28	0.42
VHA Priority code						
Low-income	35.60	38.03	31.36	35.47	33.77	34.39
Severe Disabled	14.72	14.42	34.70	28.45	32.49	26.23
Mod. Disabled	26.03	18.85	20.73	16.95	16.77	20.13
Co-pay	22.51	28.40	12.59	18.91	16.59	18.70
Missing	1.14	0.30	0.62	0.21	0.38	0.55
Total F2F visits (in FY2004)						
Less than 7	51.67	29.78	27.15	15.87	21.18	28.85
7-12 visits	32.78	34.60	32.33	28.17	23.38	30.63
13-24 visits	13.46	28.23	26.94	35.85	34.15	27.50
More than 24	2.08	7.39	13.58	20.11	21.30	13.02
Total F2F visits, mean(SD)	7.85 (6.6)	11.66 (8.4)	14.95 (19.1)	17.48 (15.1)	17.29 (15.5)	14.01 (15.0)
Diabetes-related F2F visits, mean(SD)	2.74 (2.2)	3.00 (2.6)	3.08 (2.7)	3.36 (3.28)	2.71 (3.2)	3.03 (2.8)

Abbreviations: CCIGs, Chronic comorbid illness groups; VHA, Veterans Health Administration; F2F, Face-to-face
*All patient characteristics were significantly associated with CCIG groups in bivariate analysis ($\chi 2$ test; all p-values <0.001).

Table 2.2 Veterans with incident diabetes in FY2003 who met recommended diabetes-related care guidelines and treatment goals in FY2004 by CCIGs and visit frequency (N=42,826)

Guidelines & Goals met*	CCIGs	Total annual F2F visits: Less than 7	7-12	13-24	More than 24	Total
		%	%	%	%	%
HbA1c testing (at least once 6 monthly)	None	36.99	50.23	52.43	58.43	43.86
	Concordant	38.78	49.38	53.09	54.22	47.63
	Discordant	33.11	45.50	50.26	51.77	44.27
	Both	31.99	46.51	49.27	49.12	45.72
	Dominant	22.02	35.62	40.80	40.79	35.61
Treatment goal for HbA1c (HbA1c < 8%)†	None	69.63	77.86	76.59	76.25	73.33
	Concordant	69.49	76.97	76.58	76.44	74.45
	Discordant	66.72	74.49	75.50	74.90	72.65
	Both	61.12	72.18	70.96	72.32	69.91
	Dominant	44.97	63.72	66.17	65.20	60.67
LDL-C testing (at least once yearly)	None	71.33	79.76	82.70	84.83	75.90
	Concordant	72.23	84.55	85.54	89.16	81.50
	Discordant	67.11	78.28	81.19	79.91	76.25
	Both	66.08	81.11	83.97	85.64	80.66
	Dominant	50.57	69.95	76.32	79.23	70.00
Treatment goal for LDL-C (LDL < 130 mg/dL)†	None	54.56	61.43	65.56	67.09	58.46
	Concordant	59.68	70.06	73.53	74.71	68.04
	Discordant	50.13	58.53	60.81	60.39	57.05
	Both	52.99	66.41	70.35	71.38	66.44
	Dominant	38.89	53.68	61.55	62.02	54.73
Diabetes-related F2F visit (at least once 6 monthly)	None	51.37	69.51	70.96	74.72	60.44
	Concordant	51.23	62.00	62.25	62.17	58.87
	Discordant	44.90	63.92	66.74	65.81	59.77
	Both	39.18	59.56	62.30	62.93	57.98
	Dominant	22.59	47.52	53.22	53.10	45.38

Abbreviations: CCIGs, Chronic comorbid illness groups; F2F, Face-to-face

*CCIG variable was significantly associated with all outcome variables within every F2F visit frequency stratum in bivariate analysis ($\chi 2$ test; all p-values < 0.05).

†Excluded patients whose got tested for HbA1c (n=3,310) and LDL-C (n=3,494) outside of VHA and were covered by Medicare for whom test result was not available

Table 2.3 Results from sequential multivariable logistic regression models assessing the effect of CCIGs on diabetes care (N=42,826)

		Diabetes-related care measures met				
		Process Measures			**Intermediate Measures**	
Models	**CCIG (**ref: None**)**	HbA1c testing (at least once 6 monthly)	LDL-C testing (at least once yearly)	Diabetes-related F2F visit (at least once 6 monthly)	Treatment goal for HbA1c < 8% §	Treatment goal for LDL-C < 130 mg/dL §
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Model 1*	Concordant	**1.17 (1.09-1.25)**	**1.40 (1.24-1.57)**	0.93 (0.87-1.00)	1.06 (0.96-1.17)	**1.50 (1.37-1.66)**
	Discordant	1.02 (0.97-1.07)	1.02 (0.94-1.10)	0.97 (0.92-1.02)	0.96 (0.90-1.03)	0.94 (0.89-1.01)
	Both	**1.08 (1.01-1.15)**	**1.32 (1.20-1.46)**	**0.90 (0.84-0.96)**	**0.84 (0.77-0.92)**	**1.40 (1.29-1.51)**
	Dominant	**0.71 (0.66-0.76)**	**0.74 (0.65-0.84)**	**0.54 (0.51-0.58)**	**0.56 (0.50-0.62)**	**0.86 (0.78-0.94)**
Model 2**	Concordant	**1.16 (1.08-1.24)**	**1.32 (1.18-1.47)**	0.99 (0.92-1.06)	1.01 (0.92-1.11)	**1.39 (1.27-1.52)**
	Discordant	1.04 (0.99-1.10)	1.07 (0.98-1.16)	0.98 (0.94-1.03)	1.01 (0.94-1.09)	1.00 (0.94-1.07)
	Both	**1.09 (1.03-1.17)**	**1.29 (1.17-1.42)**	0.96 (0.91-1.03)	**0.83 (0.76-0.91)**	**1.34 (1.24-1.45)**
	Dominant	**0.74 (0.69-0.80)**	**0.73 (0.65-0.82)**	**0.60 (0.56-0.64)**	**0.57 (0.52-0.63)**	**0.82 (0.75-0.90)**
Model 3***	Concordant	1.01 (0.94-1.08)	1.13 (1.00-1.27)	**0.83 (0.77-0.89)**	0.92 (0.84-1.02)	**1.25 (1.14-1.38)**
	Discordant	**0.88 (0.83-0.93)**	**0.87 (0.80-0.95)**	**0.79 (0.75-0.83)**	**0.90 (0.83-0.97)**	**0.87 (0.81-0.94)**
	Both	**0.86 (0.80-0.91)**	0.96 (0.85-1.07)	**0.70 (0.66-0.75)**	**0.70 (0.64-0.78)**	1.10 (1.01-1.20)
	Dominant	**0.59 (0.55-0.64)**	**0.56 (0.49-0.65)**	**0.46 (0.42-0.49)**	**0.50 (0.45-0.55)**	**0.68 (0.62-0.76)**

Abbreviations: CCIGs, Chronic comorbid illness groups; F2F, Face-to-face

*Model1: Unadjusted model

**Model2: Added socio-demographic covariates- age groups, gender, race, marital status, and VHA priority code to the model.

***Model3: Added covariate- total visit frequency (F2F visits). All covariates were significant independent predictors for all diabetes-related care measures.

§Excluded patients whose got tested for HbA1c (n=3,310) and LDL-C (n=3,494) outside of VHA and were covered by Medicare for whom test results was not available.

Table 2.4 Results from multivariable logistic regression models assessing the effect of interaction between CCIGs and visit frequency on diabetes care (N=42,826)

		Model 4†			
Diabetes-related care measures met	**CCIG (**ref: None**)**	**Total face-to-face visits/year**			
		Less than 7 OR (95% CI)	**7-12** OR (95% CI)	**13-24** OR (95% CI)	**More than 24** OR (95% CI)
Process Measures					
HbA1c testing (at least once 6 monthly)	Concordant	1.09 (0.97-1.22)	0.97 (0.86-1.09)	1.03 (0.89-1.19)	0.87 (0.59-1.30)
	Discordant	**0.87 (0.80-0.95)**	**0.84 (0.76-0.93)**	0.95 (0.82-1.10)	0.81 (0.56-1.15)
	Both	**0.84 (0.74-0.95)**	**0.88 (0.79-0.98)**	0.90 (0.79-1.03)	0.72 (0.50-1.02)
	Dominant	**0.55 (0.47-0.65)**	**0.58 (0.51-0.67)**	**0.65 (0.56-0.76)**	**0.52 (0.36-0.73)**
LDL-C testing (at least once yearly)	Concordant	1.01 (0.87-1.18)	**1.35 (1.14-1.59)**	1.18 (0.92-1.51)	1.40 (0.82-2.39)
	Discordant	**0.85 (0.77-0.95)**	0.97 (0.85-1.11)	0.97 (0.78-1.20)	0.78 (0.51-1.19)
	Both	**0.80 (0.69-0.92)**	1.09 (0.94-1.28)	1.08 (0.85-1.39)	1.07 (0.72-1.59)
	Dominant	**0.44 (0.38-0.51)**	**0.61 (0.50-0.75)**	**0.68 (0.53-0.87)**	0.68 (0.43-1.08)
Diabetes-related F2F visit (at least once 6 monthly)	Concordant	1.06 (0.95-1.18)	**0.76 (0.67-0.86)**	**0.72 (0.61-0.85)**	**0.62 (0.41-0.95)**
	Discordant	**0.79 (0.73-0.86)**	**0.77 (0.70-0.85)**	**0.83 (0.71-0.96)**	**0.65 (0.46-0.90)**
	Both	**0.67 (0.59-0.76)**	**0.69 (0.62-0.77)**	**0.73 (0.63-0.84)**	**0.62 (0.45-0.84)**
	Dominant	**0.34 (0.29-0.40)**	**0.45 (0.40-0.51)**	**0.51 (0.44-0.60)**	**0.42 (0.31-0.58)**
Intermediate Measures					
Treatment goal for HbA1c (HbA1c < 8%)§	Concordant	0.96 (0.83-1.11)	0.91 (0.78-1.06)	0.96 (0.80-1.16)	1.01 (0.64-1.58)
	Discordant	**0.90 (0.81-0.99)**	**0.86 (0.77-0.97)**	1.02 (0.85-1.21)	1.03 (0.69-1.54)
	Both	**0.68 (0.58-0.80)**	**0.73 (0.63-0.83)**	**0.75 (0.63-0.89)**	0.84 (0.58-1.22)
	Dominant	**0.38 (0.32-0.45)**	**0.52 (0.44-0.62)**	**0.61 (0.51-0.75)**	**0.60 (0.40-0.88)**
Treatment goal for LDL-C (LDL-C < 130 mg/dL)§	Concordant	**1.16 (1.01-1.33)**	**1.38 (1.20-1.60)**	**1.32 (1.10-1.59)**	1.31 (0.88-1.95)
	Discordant	**0.87 (0.79-0.96)**	0.95 (0.85-1.07)	0.88 (0.75-1.03)	0.85 (0.61-1.19)
	Both	0.92 (0.81-1.04)	**1.21 (1.06-1.38)**	1.19 (0.99-1.42)	1.21 (0.88-1.66)
	Dominant	**0.52 (0.45-0.61)**	**0.72 (0.61-0.86)**	**0.81 (0.67-0.99)**	0.77 (0.54-1.11)

Abbreviations: CCIGs, Chronic comorbid illness groups; F2F, Face-to-face

†Model4: Added the interaction term between CCIGs and visit frequency (CCIG*F2F visits) to the model 3. The interaction term (CCIG* F2F visits) was significant for all diabetes care measures, except for HbA1c testing.

§Excluded patients whose got tested for HbA1c (n=3,310) and LDL-C (n=3,494) outside of VHA and were covered by Medicare for whom test results was not available.

Table 3.1 Characteristics of veterans who initiated anti-diabetic medication therapy in FY2000-02*(N=79,249)

	Chronic comorbid illness groups									
	None-None	**None-Other**	**Conc.-Conc.**	**Conc.-Other**	**Disc.-Disc.**	**Disc.-Other**	**Both-Both**	**Both-Other**	**Dominant**	**All**
N	7,915	25,652	3,681	6,201	10,071	12,124	6,797	2,305	4,503	79,249
%	9.99%	32.37%	4.64%	7.82%	12.71%	15.30%	8.58%	2.91%	5.68%	100.0%
Age (yrs) Mean(SD)	64.7 (12.2)	63.4 (11.5)	70.2 (9.3)	68.0 (9.8)	58.4 (11.4)	61.3 (11.0)	66.3 (10.6)	68.0 (10.1)	67.8 (11.0)	63.9 (11.6)
Male	97.2	97.2	99.1	98.8	94.7	96.4	98.3	98.3	96.6	97.1
White	71.3	69.4	88.2	82.8	71.1	73.7	85.4	84.5	81.0	74.9
Non-White	18.1	21.7	9.8	14.8	21.9	22.0	13.3	14.7	17.6	19.2
Missing	10.6	8.9	2.0	2.4	7.0	4.3	1.3	0.9	1.4	6.0
Married**	66.3	62.1	70.5	66.1	56.5	57.1	62.9	63.2	59.7	61.7
VHA Priority Status**										
Co-Pay	32.5	22. 8	30.7	19.8	12.7	10.5	13.5	10.5	12.2	19.0
Low Income	37.4	41.1	43.0	46.1	35.7	37.7	42.8	41.7	40.1	40.1
Mod. Disabled	21.7	24.1	15.7	19.5	23.8	22.7	19.7	20.1	18.1	22.0
Severe Disabled	7.6	11.4	10.3	14.3	26.9	28.7	23.7	27.4	29.5	18.3

Baseline HbA1c	8.11 (2.08)	8.23 (2.09)	7.83 (1.72)	7.92 (1.79)	8.12 (2.07)	8.12 (1.99)	7.80 (1.74)	7.79 (1.72)	7.90 (1.87)	8.07 (1.98)
Baseline BMI	31.2 (5.7)	31.7 (6.0)	30.5 (5.5)	31.3 (5.7)	32.7 (6.3)	32.6 (6.3)	32.2 (6.3)	31.6 (5.8)	30.1 (5.8)	31.77 (5.8)
Change from baseline BMI	-0.8 (2.6)	-1.1 (3.2)	-1.0 (2.6)	-1.5 (3.2)	-1.1 (3.2)	-1.3 (3.6)	-1.2 (3.2)	-2.2 (3.5)	-1.5 (3.3)	-1.8 (3.2)
Non-DMF2F visits in BY1 Median (Q1-Q3)	2 (0-4)	2 (1-5)	4 (2-8)	6 (3-11)	7 (4-14)	8 (4-15)	9 (5-17)	12 (6-20)	11 (6-20)	5 (2-10)
DMF2F visits in BY1 Median (Q1-Q3)	1 (1-2)	1 (1-2)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-4)	2 (1-4)	2 (1-3)	2 (1-3)
Non_DM Meds in BY1 (mean(s.d.))	2.4 (2.5)	2.6 (2.7)	4.7 (3.1)	5.1 (3.3)	4.8 (3.8)	5.0 (4.0)	7.2 (4.6)	7.2 (4.8)	5.4 (4.3)	4.2 (3.8)
Deceased	22.9	21.7	42.54	35.3	19.8	25.5	41.4	51.1	54.8	28.6
Years in Study Median (IQR)	7.5 (2.7-9.1)	8.8 (7.0-9.8)	6.2 (2.7-8.8)	8.5 (5.8-9.6)	8.6 (5.7-9.6)	8.8 (7.3-9.8)	8.1 (3.8-9.2)	8.0 (4.8-9.2)	6.0 (2.7-8.8)	8.5 (5.3-9.6)

*Data presented as proportions, unless indicated otherwise **Those with missing values (ranged between 0.21%-0.99%) not shown here.
Abbreviations: CCIGs, Chronic comorbid illness groups; NA, Not Applicable; VHA, Veterans Health Administration; Non-DMF2F, Non-diabetes related face-to-face; DMF2F, diabetes-related face-to-face; Non_DMMeds, number of non-diabetes medication classes; BY1, Baseline year 1; BMI, Body mass index

Table 3.2 Selected utilization and glycemic control measures by chronic comorbid illness groups (N=79,249)

	Chronic comorbid illness groups									
	None None	**None Other**	**Conc. Conc.**	**Conc. Other**	**Disc. Disc.**	**Disc. Other**	**Both Both**	**Both Other**	**Dominant**	**All**
Average annual non-DMF2F visits*	1 (0-3)	4 (2-7)	2 (1-5)	6 (3-10)	5 (2-9)	7 (4-13)	6 (3-11)	10 (6-17)	7 (4-14)	4 (2-9)
Average annual DMF2F visits*	2 (1-3)	3 (2-4)	2 (2-3)	3 (2-5)	3 (2-4)	4 (3-5)	3 (2-5)	4 (3-5)	3 (2-5)	3 (2-4)
Average annual HbA1c tests*	1.4 (0.9-1.9)	1.7 (1.2-2.1)	1.5 (1.0-2.0)	1.7 (1.3-2.2)	1.7 (1.2-2.1)	1.8 (1.3-2.2)	1.7 (1.2-2.2)	1.8 (1.3-2.2)	1.6 (1.0-2.1)	1.7 (1.2-2.1)
At veteran's level: Proportion of HbA1c < 6%**	0.16 (0.28)	0.15 (0.25)	0.16 (0.27)	0.16 (0.25)	0.18 (0.27)	0.18 (0.26)	0.18 (0.27)	0.21 (0.28)	0.23 (0.31)	0.17 (0.27)
Proportion of HbA1c > 9%**	0.12 (0.24)	0.12 (0.21)	0.08 (0.18)	0.08 (0.16)	0.12 (0.20)	0.11 (0.19)	0.08 (0.17)	0.07 (0.15)	0.09 (0.19)	0.11 (0.20)
Within CCIG_CCIG groups: Proportion with at least 1 HbA1c <6%*	38.9	47.7	42.1	52.3	51.0	55.7	49.5	57.3	54.0	49.3
Proportion with at least 1 HbA1c >9%*	33.3	44.9	27.9	37.3	43.7	46.0	34.2	34.0	31.3	40.4

*Median (Q1-Q3);**Mean (s.d.);

Abbreviations: non-DMF2F, non-diabetes related face-to-face; DMF2F, diabetes-related face-to-face;

Table 3.3 Relationship between chronic comorbid illness groups and HbA1c trends. Results from piecewise linear random effects models (n=79,249)

	Unadjusted results						**Adjusted results**					
Chronic comorbid illness groups	**Annualized slope AB (Baseline to 6 months)**		**Intercept/Point B (At end of 6 months)**		**Annualized slope BC (Post 6 months)**		**Annualized slope AB (Baseline to 6 months)**		**Intercept/Point B (At end of 6 months)**		**Annualized slope BC (Post 6 months)**	
	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig
None_None	-2.350 (0.036)	ref	6.849 (0.016)	ref	0.071 (0.003)	ref	-2.338 (0.036)	ref	7.130 (0.023)	ref	0.073 (0.003)	ref
	Contrasted with reference group (None_None)						Contrasted with reference group (None_None)					
None_Other	0.018 (0.041)	NS	0.142 (0.018)	***	-0.017 (0.003)	***	0.040 (0.040)	NS	0.101 (0.017)	***	-0.013 (0.003)	***
Conc_Conc	0.361 (0.062)	***	-0.093 (0.029)	**	-0.016 (0.005)	**	0.333 (0.062)	***	0.099 (0.027)	***	-0.014 (0.005)	**
Conc_Other	0.190 (0.052)	***	-0.076 (0.024)	**	-0.021 (0.004)	***	0.189 (0.051)	***	0.069 (0.022)	**	-0.016 (0.004)	***
Disc_Disc	-0.167 (0.047)	***	-0.080 (0.021)	***	0.010 (0.004)	**	-0.172 (0.046)	***	-0.184 (0.020)	***	0.012 (0.004)	***
Disc_Other	-0.043 (0.045)	NS	-0.002 (0.020)	NS	-0.011 (0.003)	**	-0.037 (0.044)	NS	-0.043 (0.019)	*	-0.005 (0.003)	NS
Both_Both	0.421 (0.051)	***	-0.094 (0.023)	***	-0.016 (0.004)	***	0.399 (0.050)	***	0.052 (0.022)	*	-0.013 (0.004)	**
Both_Other	0.428 (0.070)	***	-0.124 (0.033)	***	-0.037 (0.006)	***	0.407 (0.070)	***	0.070 (0.031)	*	-0.029 (0.006)	***
Dominant	0.012 (0.058)	NS	-0.235 (0.027)	***	-0.019 (0.005)	***	-0.012 (0.057)	NS	-0.099 (0.025)	***	-0.016 (0.005)	***

P-values (significance) - <0.001(***); <0.01 (**); <0.05(*); =>0.05(NS)

Model adjusted for age groups, race/ethnicity, marital status, VHA priority status, seasonal variation (sine & cosine terms), baseline HbA1c, baseline body mass index (BMI), annual change in BMI relative to baseline BMI, non diabetes-related face-to-face visits, diabetes-related face-to-face visits, and type of diabetes-medication; change in BMI, visits and diabetes medication variables were updated annually and treated as time-varying covariates in the models.

Table 3.4 Stratified analyses by age groups: Adjusted relationship between chronic comorbid illness groups and HbA1c trends. Results from piecewise linear random effects models

Chronic comorbid illness groups	**Annualized slope AB (Baseline to 6 months)**		**Intercept/Point B (At end of 6 months)**		**Annualized slope BC (Post 6 months)**		**Annualized slope AB (Baseline to 6 months)**		**Intercept/Point B (At end of 6 months)**		**Annualized slope BC (Post 6 months)**	
	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig
	Age Group: Under 55 years (n=20,255)						**Age Group: 55 to <65 years (n=18,408)**					
None_None (ref)	-3.126 (0.088)	ref	7.031 (0.062)	ref	0.115 (0.007)	ref	-2.621 (0.075)	ref	6.768 (0.006)	ref	0.073 (0.006)	ref
	Contrasted with reference group (None_None)						Contrasted with reference group (None_None)					
None_Other	0.453 (0.099)	***	0.286 (0.043)	***	-0.039 (0.007)	***	0.084 (0.084)	NS	0.112 (0.036)	**	-0.014 (0.006)	*
Conc_Conc	1.002 (0.238)	***	0.165 (0.105)	NS	-0.035 (0.018)	NS	0.198 (0.141)	NS	0.111 (0.061)	NS	-0.005 (0.011)	NS
Conc_Other	0.837 (0.160)	***	0.185 (0.070)	**	-0.030(0.011)	**	0.310 (0.109)	**	0.058 (0.047)	NS	-0.009 (0.008)	NS
Disc_Disc	0.357 (0.104)	***	-0.104 (0.046)	*	-0.019 (0.008)	*	0.109 (0.093)	NS	-0.125 (0.041)	**	0.012 (0.007)	NS
Disc_Other	0.581 (0.104)	***	0.111 (0.047)	*	-0.038 (0.008)	***	0.118 (0.090)	NS	-0.051 (0.039)	NS	-0.001 (0.007)	NS
Both_Both	0.975 (0.135)	***	0.087 (0.060)	NS	-0.023 (0.010)	*	0.816 (0.104)	***	0.123 (0.045)	**	-0.018 (0.008)	*
Both_Other	1.469 (0.226)	***	0.020 (0.098)	NS	-0.045 (0.016)	**	0.607 (0.153)	***	0.099 (0.066)	NS	-0.026 (0.012)	*
Dominant	0.666 (0.162)	***	-0.162 (0.072)	*	-0.025 (0.012)	*	0.192 (0.123)	NS	-0.096 (0.054)	NS	-0.014 (0.006)	NS
	Age Group: 65 to <75 years (n=23,380)						**Age Group: 75 years or more (n=17,206)**					
None_None (ref)	-2.005 (0.053)	ref	6.645 (0.030)	ref	0.055(0.004)	ref	-1.562 (0.061)	ref	6.684 (0.032)	ref	0.042 (0.006)	ref
	Contrasted with reference group (None_None)						Contrasted with reference group (None_None)					
None_Other	-0.121 (0.060)	*	0.048 (0.025)	NS	-0.003 (0.005)	NS	-0.159 (0.069)	*	-0.042 (0.030)	NS	0.005 (0.007)	NS
Conc_Conc	0.075 (0.085)	NS	0.058 (0.036)	NS	0.006 (0.007)	NS	-0.203 (0.090)	*	-0.058 (0.039)	NS	0.004 (0.009)	NS
Conc_Other	-0.139 (0.072)	NS	0.017 (0.031)	NS	-0.004 (0.006)	NS	-0.356 (0.080)	***	-0.080 (0.035)	*	0.006 (0.008)	NS
Disc_Disc	-0.218 (0.077)	**	-0.130 (0.033)	***	0.013 (0.006)	*	-0.427 (0.094)	***	-0.207 (0.041)	***	0.018 (0.010)	NS
Disc_Other	-0.279 (0.069)	***	-0.034 (0.029)	NS	-0.002 (0.005)	NS	-0.378 (0.080)	***	-0.159 (0.035)	***	0.022 (0.008)	**
Both_Both	0.120 (0.074)	NS	0.043 (0.032)	NS	-0.008 (0.006)	NS	-0.357 (0.082)	***	-0.129 (0.036)	***	0.013 (0.009)	NS
Both_Other	-0.057 (0.097)	NS	0.021 (0.042)	NS	-0.016 (0.008)	NS	-0.209 (0.103)	*	-0.081 (0.046)	NS	0.003 (0.010)	NS
Dominant	-0.363 (0.084)	***	-0.081 (0.036)	*	-0.016 (0.007)	*	-0.582 (0.086)	***	-0.249 (0.038)	***	0.017 (0.010)	NS

P-values (significance) - <0.001(***); <0.01 (**); <0.05(*); =>0.05(NS)

Models were adjusted for age groups, race/ethnicity, marital status, VHA priority status, seasonal variation (sine & cosine terms), baseline HbA1c, baseline body mass index (BMI), annual change in BMI relative to baseline BMI, non diabetes-related face-to-face visits, diabetes-related face-to-face visits, and type of diabetes-medication; change in BMI, visits and diabetes medication variables were updated annually and treated as time-varying covariates in the models.

Table 3.5 HbA1c trends study: Results from 4 Sensitivity Analyses

Chronic comorbid illness groups	**Annualized slope AB (Baseline to 6 months)**		**Intercept/Point B (At end of 6 months)**		**Annualized slope BC (Post 6 months)**		**Annualized slope AB (Baseline to 6 months)**		**Intercept/Point B (At end of 6 months)**		**Annualized slope BC (Post 6 months)**	
	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig	Estimate (S.E.)	sig
	Baseline HbA1c > 7 (n=35,261)						**Baseline HbA1c > 8 (n=20,550)**					
None_None (ref)	-3.686 (0.049)	ref	7.102 (0.034)	ref	0.080 (0.004)	ref	-5.413 (0.075)	ref	7.327 (0.048)	ref	0.088 (0.006)	ref
	Contrasted with reference group (None_None)						Contrasted with reference group (None_None)					
None_Other	0.092 (0.056)	NS	0.105 (0.026)	***	-0.023 (0.005)	***	0.307 (0.079)	***	0.158 (0.036)	***	-0.033 (0.007)	***
Conc_Conc	0.605 (0.085)	***	0.150 (0.040)	***	-0.024 (0.008)	**	0.636 (0.126)	***	0.136 (0.059)	*	-0.030 (0.011)	*
Conc_Other	0.387 (0.071)	***	0.074 (0.033)	*	-0.028 (0.006)	***	0.466 (0.103)	***	0.073 (0.048)	NS	-0.040 (0.009)	***
Disc_Disc	-0.223 (0.064)	***	-0.153 (0.030)	***	0.001 (0.005)	NS	-0.223 (0.090)	*	-0.178 (0.042)	***	-0.007 (0.008)	NS
Disc_Other	0.060 (0.061)	NS	0.026 (0.029)	NS	-0.014 (0.005)	**	0.180 (0.086)	*	-0.014 (0.041)	NS	-0.025 (0.007)	***
Both_Both	0.644 (0.070)	***	0.128 (0.033)	***	-0.030 (0.006)	***	0.721 (0.102)	***	0.130 (0.048)	**	-0.044 (0.009)	***
Both_Other	0.627 (0.097)	***	0.148 (0.046)	**	-0.049 (0.009)	***	0.713 (0.144)	***	0.134 (0.067)	*	-0.055 (0.013)	***
Dominant	0.074 (0.079)	NS	-0.051 (0.037)	NS	-0.027 (0.007)	***	0.071 (0.115)	NS	-0.074 (0.054)	NS	-0.036 (0.010)	***
	Limited to those with a baseline HbA1c (n=52,827)						**Limited to those survived till end of study (n=46,148)**					
None_None (ref)	-2.502 (0.038)	ref	7.053 (0.026)	ref	0.086 (0.004)	ref	-2.486 (0.049)	ref	7.074(0.031)	ref	0.078 (0.003)	ref
	Contrasted with reference group (None_None)						Contrasted with reference group (None_None)					
None_Other	0.068 (0.043)	NS	0.106 (0.021)	***	-0.019 (0.004)	***	0.144 (0.054)	***	0.141 (0.023)	***	-0.014 (0.004)	***
Conc_Conc	0.420 (0.066)	***	0.143 (0.032)	***	-0.021 (0.006)	***	0.366 (0.091)	***	0.153 (0.039)	***	-0.020 (0.006)	**
Conc_Other	0.261 (0.055)	***	0.093 (0.026)	***	-0.024 (0.005)	***	0.434 (0.068)	***	0.119 (0.030)	***	-0.017 (0.004)	***
Disc_Disc	-0.108 (0.049)	*	-0.120 (0.024)	***	0.000 (0.004)	NS	-0.081 (0.060)	NS	-0.141 (0.026)	***	0.009 (0.004)	*
Disc_Other	0.017 (0.047)	NS	-0.010 (0.023)	NS	-0.012 (0.004)	**	0.173 (0.058)	**	0.020 (0.025)	NS	-0.009 (0.004)	*
Both_Both	0.507 (0.054)	***	0.115 (0.026)	***	-0.024 (0.005)	***	0.584 (0.069)	***	0.066 (0.030)	*	-0.014 (0.005)	**
Both_Other	0.525 (0.074)	***	0.152 (0.035)	***	-0.043 (0.007)	***	0.677 (0.101)	***	0.092 (0.044)	*	-0.032 (0.007)	***
Dominant	0.057 (0.061)	NS	-0.047 (0.036)	NS	-0.027 (0.006)	***	0.058 (0.084)	NS	-0.016 (0.037)	NS	-0.020 (0.007)	***

P-values (significance) - <0.001(***); <0.01 (**); <0.05(*); =>0.05(NS)

Models were adjusted for age groups, race/ethnicity, marital status, VHA priority status, seasonal variation (sine and cosine terms), baseline HbA1c, baseline body mass index (BMI), annual change in BMI relative to baseline BMI, non diabetes-related face-to-face visits, diabetes-related face-to-face visits, and type of diabetes-medication; change in BMI, visits and diabetes medication variables were updated annually and treated as time-varying covariates in the models.

Descriptive statistics: Please refer to Table 3.1 from the HbA1c trends study for study cohort description.

Table 4.1 Diabetes medication adherence levels (measured using proportion of days covered (PDC)) across the chronic comorbidity illness groups (N=77,466)

	Adherence (%) (4 PDC levels)				Adherence (%) (2 PDC levels)	
CCIG*_CCIG	**Poor (<0.60)**	**Moderate (0.6 to < 0.8)**	**Good (0.8 to < 0.9)**	**Excellent (=>0.9)**	**No (< 0.8)**	**Yes (=> 0.8)**
None_None	20.34	28.14	25.57	25.95	48.48	51.52
None_Other	20.23	32.79	26.56	20.43	53.02	46.98
Concordant_Concordant	16.00	28.46	26.14	29.4	44.46	55.54
Concordant_Other	16.06	31.22	30.23	22.49	47.27	52.73
Discordant_Discordant	20.50	30.45	25.07	23.98	50.95	49.05
Discordant_Other	19.68	32.82	26.42	21.07	52.51	47.49
Both_Both	15.87	29.70	27.05	27.37	45.58	54.42
Both_other	16.71	34.48	26.88	21.93	51.19	48.81
Dominant	19.57	31.14	23.62	25.66	50.71	49.29
All	19.16	31.42	26.41	23.01	50.58	49.42

*Abbreviations: CCIG, Chronic comorbid illness group

Table 4.2 Relationship between type of chronic comorbidity and diabetes medication adherence (adherent defined as PDC =>0.80) (N=77,466)

	Unadjusted ORs with 95% CIs	**Adjusted* ORs with 95% CIs**
CCIG_CCIG (ref: None_None)		
None_Other	**0.83 (0.79-0.88)**	**0.81 (0.77-0.86)**
Concordant_Concordant	**1.18 (1.09-1.27)**	0.92 (0.85-1.00)
Concordant_Other	1.05 (0.98-1.12)	**0.84 (0.78-0.90)**
Discordant_Discordant	**0.91 (0.85-0.96)**	**0.88 (0.82-0.94)**
Discordant_Other	**0.85 (0.80-0.90)**	**0.77 (0.72-0.82)**
Both_Both	**1.12 (1.05-1.20)**	**0.83 (0.77-0.89)**
Both_other	**0.90 (0.82-0.99)**	**0.68 (0.61-0.75)**
Dominant	**0.91 (0.85-0.99)**	**0.78 (0.72-0.84)**

Abbreviations: PDC, proportion of days covered

*Adjusted for age categories, gender, race/ethnicity, marital status, Veterans Health Administration (VHA) priority code, average annual non diabetes-related face-to-face visits, average annual diabetes-related face-to-face visits, average annual non-diabetes medication classes, baseline body mass index (BMI) category, change in BMI from baseline, and insulin use status.

Table 4.3 Results from the final model examining the relationship between type of chronic comorbidity and diabetes medication adherence (adherent defined as PDC=>0.8) (N=77,466)

Adjusted odds ratios			
	OR	95% Confidence Limits	
None_Other vs. None_None	0.81	0.77	0.86
Concordant_Concordant vs. None_None	0.92	0.85	1.00
Concordant_Other vs. None_None	0.84	0.78	0.90
Discordant_Discordant vs. None_None	0.88	0.82	0.94
Discordant_Other vs. None_None	0.77	0.72	0.82
Both_Both vs. None_None	0.83	0.77	0.89
Both_Other vs. None_None	0.68	0.61	0.75
Dominant vs. None_None	0.78	0.72	0.84
55-64 vs. Under 55 years	1.31	1.26	1.37
65-74 vs. Under 55 years	1.42	1.35	1.48
Over 75 vs. Under 55 years	1.44	1.37	1.51
Female vs. Male	0.84	0.76	0.92
Black vs. White	0.49	0.47	0.51
Missing Race vs. White	0.85	0.80	0.91
Other vs. White	0.67	0.63	0.72
Miss Marital vs. Married	1.05	0.82	1.36
Not Married vs. Married	0.87	0.85	0.90
Low Income vs. Co-Pay	0.83	0.79	0.86
Miss Priority vs. Co-Pay	1.10	0.90	1.36
Mod Disabled vs. Co-Pay	0.89	0.85	0.93
Severe Disabled vs. Co-Pay	1.01	0.96	1.06
Average_Annual_Non_DMF2F > 12 vs. <= 4 visits	0.78	0.74	0.82
Average _Annual_Non_DMF2F 9-12 vs. <= 4 visits	0.81	0.77	0.86
Average _Annual_Non_DMF2F 5-8 vs. <= 4 visits	0.85	0.82	0.89
Average _Annual_DMF2F > 4 vs. <= 2 visits	1.35	1.29	1.42
Average _Annual_DMF2F 3-4 vs. <= 2 visits	1.25	1.21	1.30
Over Wt vs. Under/Normal Wt*	1.10	1.04	1.16
Obese vs. Under/Normal Wt	1.18	1.11	1.24
Morbid Obese vs. Under/Normal Wt	1.24	1.17	1.31
BMI Change (Final-Baseline)	1.05	1.04	1.05
Insulin Use (Yes vs. No)	0.60	0.58	0.62
Average_Annual_NonDMMeds > 12 vs. <= 4	2.19	2.06	2.33
Average_Annual_NonDMMeds 9-12 vs. <= 4	1.80	1.71	1.89
Average_Annual_NonDMMeds 5-8 vs. <= 4	1.39	1.33	1.44

Abbreviations: Non_DMF2F, Non diabetes-related face-to-face; DMF2F, Diabetes-related face-to-face; NonDMDMeds, number of non-diabetes medication classes; BMI, Body mass index; PDC, proportion of days covered; Wt, Weight

*BMI categories: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 4.4 Diabetes medication adherence study sensitivity analyses: Using PDC => 0.7 as cut-off for defining adherence (N=77,466)

Adjusted odds ratios			
		95%	
	OR	Confidence Limits	
None_Other vs. None_None	0.87	0.82	0.92
Concordant_Concordant vs. None_None	0.92	0.84	1.01
Concordant_Other vs. None_None	0.85	0.78	0.92
Discordant_Discordant vs. None_None	0.92	0.86	0.98
Discordant_Other vs. None_None	0.80	0.75	0.86
Both_Both vs. None_None	0.84	0.78	0.91
Both_Other vs. None_None	0.79	0.70	0.87
Dominant vs. None_None	0.81	0.74	0.88
55-64 vs. Under 55 years	1.34	1.28	1.40
65-74 vs. Under 55 years	1.50	1.43	1.57
Over 75 vs. Under 55 years	1.59	1.51	1.67
Female vs. Male	0.81	0.74	0.89
Black vs. White	0.50	0.48	0.52
Missing Race vs. White	0.84	0.78	0.90
Other vs. White	0.64	0.60	0.69
Miss Marital vs. Married	1.14	0.87	1.51
Not Married vs. Married	0.85	0.83	0.88
Low Income vs. Co-Pay	0.78	0.74	0.81
Miss Priority vs. Co-Pay	1.07	0.85	1.34
Mod Disabled vs. Co-Pay	0.83	0.79	0.88
Severe Disabled vs. Co-Pay	0.96	0.91	1.01
Average_Annual_Non_DMF2F > 12 vs. <= 4 visits	0.74	0.70	0.78
Average _Annual_Non_DMF2F 9-12 vs. <= 4 visits	0.82	0.77	0.87
Average _Annual_Non_DMF2F 5-8 vs. <= 4 visits	0.86	0.82	0.90
Average _Annual_DMF2F > 4 vs. <= 2 visits	1.62	1.54	1.70
Average _Annual_DMF2F 3-4 vs. <= 2 visits	1.42	1.37	1.48
Over Wt vs. Under/Normal Wt*	1.19	1.12	1.26
Obese vs. Under/Normal Wt	1.25	1.18	1.33
Morbid Obese vs. Under/Normal Wt	1.34	1.26	1.43
BMI Change (Final-Baseline)	1.05	1.04	1.05
Insulin Use (Yes vs. No)	0.67	0.65	0.70
Average_Annual_NonDMMeds > 12 vs. <= 4	2.47	2.31	2.63
Average_Annual_NonDMMeds 9-12 vs. <= 4	1.96	1.86	2.07
Average_Annual_NonDMMeds 5-8 vs. <= 4	1.50	1.44	1.56

Abbreviations: Non_DMF2F, Non diabetes-related face-to-face; DMF2F, Diabetes-related face-to-face; NonDMDMeds, number of non-diabetes medication classes; BMI, Body mass index; PDC, proportion of days covered; Wt, Weight

*BMI categories: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 4.5 Diabetes medication adherence study sensitivity analyses: Using PDC => 0.9 as cut-off for defining adherence (N=77,466)

Adjusted odds ratios			
		95%	
	OR	Confidence Limits	
None_Other vs. None_None	0.78	0.73	0.83
Concordant_Concordant vs. None_None	1.03	0.94	1.12
Concordant_Other vs. None_None	0.76	0.70	0.82
Discordant_Discordant vs. None_None	0.91	0.85	0.98
Discordant_Other vs. None_None	0.76	0.70	0.82
Both_Both vs. None_None	0.87	0.81	0.95
Both_Other vs. None_None	0.68	0.61	0.77
Dominant vs. None_None	0.91	0.83	0.99
55-64 vs. Under 55 years	1.25	1.19	1.32
65-74 vs. Under 55 years	1.29	1.22	1.36
Over 75 vs. Under 55 years	1.26	1.19	1.34
Female vs. Male	0.88	0.78	0.99
Black vs. White	0.48	0.45	0.51
Missing Race vs. White	0.90	0.84	0.98
Other vs. White	0.68	0.63	0.75
Miss Marital vs. Married	1.03	0.76	1.39
Not Married vs. Married	0.92	0.88	0.95
Low Income vs. Co-Pay	0.92	0.88	0.97
Miss Priority vs. Co-Pay	1.20	0.95	1.52
Mod Disabled vs. Co-Pay	0.96	0.91	1.02
Severe Disabled vs. Co-Pay	1.16	1.09	1.23
Average_Annual_Non_DMF2F > 12 vs. <= 4 visits	0.78	0.74	0.83
Average _Annual_Non_DMF2F 9-12 vs. <= 4 visits	0.83	0.78	0.89
Average _Annual_Non_DMF2F 5-8 vs. <= 4 visits	0.84	0.80	0.88
Average _Annual_DMF2F > 4 vs. <= 2 visits	1.10	1.04	1.16
Average _Annual_DMF2F 3-4 vs. <= 2 visits	1.04	0.997	1.08
Over Wt vs. Under/Normal Wt*	1.04	0.97	1.10
Obese vs. Under/Normal Wt	1.06	0.997	1.14
Morbid Obese vs. Under/Normal Wt	1.10	1.03	1.18
BMI Change (Final-Baseline)	1.05	1.04	1.05
Insulin Use (Yes vs. No)	0.58	0.55	0.60
Average_Annual_NonDMMeds > 12 vs. <= 4	2.06	1.93	2.21
Average_Annual_NonDMMeds 9-12 vs. <= 4	1.51	1.43	1.60
Average_Annual_NonDMMeds 5-8 vs. <= 4	1.19	1.13	1.25

Abbreviations: Non_DMF2F, Non diabetes-related face-to-face; DMF2F, Diabetes-related face-to-face; NonDMDMeds, number of non-diabetes medication classes; BMI, Body mass index; PDC, proportion of days covered; Wt, Weight

*BMI categories: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 4.6 Diabetes medication adherence study sensitivity analyses: Using PDC results generated by analyzing refills for oral anti-diabetic agents only (N=77,466)

Adjusted odds ratios			
		95%	
	OR	Confidence Limits	
None_Other vs. None_None	0.81	0.76	0.85
Concordant_Concordant vs. None_None	0.91	0.84	1.00
Concordant_Other vs. None_None	0.83	0.77	0.89
Discordant_Discordant vs. None_None	0.87	0.81	0.92
Discordant_Other vs. None_None	0.78	0.73	0.83
Both_Both vs. None_None	0.82	0.77	0.89
Both_Other vs. None_None	0.68	0.61	0.75
Dominant vs. None_None	0.78	0.72	0.84
55-64 vs. Under 55 years	1.34	1.28	1.39
65-74 vs. Under 55 years	1.49	1.42	1.56
Over 75 vs. Under 55 years	1.50	1.42	1.57
Female vs. Male	0.82	0.75	0.90
Black vs. White	0.49	0.47	0.52
Missing Race vs. White	0.87	0.81	0.93
Other vs. White	0.67	0.63	0.71
Miss Marital vs. Married	1.11	0.86	1.44
Not Married vs. Married	0.86	0.83	0.89
Low Income vs. Co-Pay	0.81	0.77	0.84
Miss Priority vs. Co-Pay	1.11	0.90	1.37
Moderately disabled vs. Co-Pay	0.86	0.82	0.90
Severely disabled vs. Co-Pay	0.99	0.94	1.05
Average_Annual_Non_DMF2F > 12 vs. <= 4 visits	0.77	0.73	0.81
Average _Annual_Non_DMF2F 9-12 vs. <= 4 visits	0.81	0.76	0.85
Average _Annual_Non_DMF2F 5-8 vs. <= 4 visits	0.84	0.81	0.88
Average _Annual_DMF2F > 4 vs. <= 2 visits	1.42	1.36	1.49
Average _Annual_DMF2F 3-4 vs. <= 2 visits	1.28	1.24	1.33
Over Wt vs. Under/Normal Wt*	1.09	1.04	1.16
Obese vs. Under/Normal Wt	1.17	1.11	1.24
Morbid Obese vs. Under/Normal Wt	1.20	1.13	1.27
BMI Change (Final-Baseline)	1.04	1.04	1.05
Insulin Use (Yes vs. No)	0.90	0.87	0.93
Average_Annual_NonDMMeds > 12 vs. <= 4	2.30	2.17	2.44
Average_Annual_NonDMMeds 9-12 vs. <= 4	1.83	1.75	1.92
Average_Annual_NonDMMeds 5-8 vs. <= 4	1.40	1.35	1.46

Abbreviations: Non_DMF2F, Non diabetes-related face-to-face; DMF2F, Diabetes-related face-to-face; NonDMDMeds, number of non-diabetes medication classes; BMI, Body mass index; PDC, proportion of days covered; Wt, Weight

*BMI categories: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 4.7 Type of chronic comorbidity and non-persistence with diabetes medications (using 60-day treatment gap as definition for non-persistence) during the first 2 years following treatment initiation for diabetes (N=79,246)

			Time to first diabetes medication treatment gap (in months)
CCIG	**Persistent %**	**Non_persistent %**	Mean (s.d.)
None	40.28	59.72	14.25 (8.91)
Concordant	43.65	56.35	14.98 (8.79)
Discordant	41.11	58.89	14.74 (8.86)
Both	44.90	55.10	15.02 (8.71)
Dominant	39.93	60.07	13.49 (8.83)
All	41.44	58.65	14.52 (8.86)

Abbreviations: CCIGs, Chronic comorbid illness groups

Table 4.8 Relationship between type of chronic comorbidity and non-persistence* with diabetes medication during the first 2 years following treatment initiation for diabetes (N=79,246)

	Unadjusted HRs with 95% CIs	**Adjusted** HRs with 95% CIs**
CCIG (ref: None)		
Concordant	**0.90 (0.87-0.93)**	0.97 (0.94-1.00)
Discordant	**0.96 (0.94-0.98)**	0.99 (0.97-1.01)
Both Conc_Disc	**0.88 (0.85-0.90)**	0.98 (0.95-1.02)
Dominant	**1.06 (1.01-1.10)**	**1.12 (1.08-1.17)**

Abbreviations: CCIGs, Chronic comorbid illness groups; HR, Hazard Ratios

*Non-persistence defined as 60 or more days of treatment gap.

**Adjusted for age categories, race/ethnicity, marital status, Veterans Health Administration (VHA) priority code, incident CCIGs, number of non-diabetes medication classes, body mass index (BMI) category, and HbA1c category.

Table 4.9 Results from the final modal examining the relationship between type of chronic comorbidity and non_persistence* with diabetes medication during the first 2 years following treatment initiation for diabetes (N=79,246)

Adjusted Hazard Ratios (HR)			
			95%
	HR	Confidence Limits	
Concordant vs. None	0.97	0.94	1.00
Discordant vs. None	0.99	0.97	1.01
Both Conc_Disc vs. None	0.98	0.95	1.02
Dominant vs. None	1.12	1.08	1.17
Incident Concordant vs. Incident None	0.99	0.95	1.02
Incident Discordant vs. Incident None	1.01	0.98	1.04
Incident Both Conc_Disc vs. Incident None	1.03	0.96	1.09
Incident Dominant vs. Incident None	1.13	1.09	1.18
55-64 vs. Under 55 years	0.86	0.84	0.89
65-74 vs. Under 55 years	0.88	0.85	0.90
Over 75 vs. Under 55 years	0.92	0.90	0.95
Black vs. White	1.34	1.31	1.38
Missing Race vs. White	1.10	1.05	1.14
Other vs. White	1.25	1.20	1.30
Miss Marital vs. Married	0.94	0.79	1.10
Not Married vs. Married	1.10	1.08	1.12
Low Income vs. Co-Pay	1.12	1.09	1.15
Miss Priority vs. Co-Pay	0.99	0.87	1.13
Moderately disabled vs. Co-Pay	1.11	1.08	1.14
Severely disabled vs. Co-Pay	1.03	0.996	1.06
NonDMMeds > 12 vs. <= 4	0.76	0.72	0.80
NonDMMeds 9-12 vs. <= 4	0.81	0.78	0.84
NonDMMeds 05-8 vs. <= 4	0.87	0.85	0.89
Over Wt vs. Under/Normal Wt**	0.89	0.86	0.92
Obese vs. Under/Normal Wt	0.85	0.83	0.88
Morbid Obese vs. Under/Normal Wt	0.82	0.79	0.85
Miss BMI vs. Under/Normal Wt	0.98	0.88	1.08
Baseline HbA1c (=>9%) vs. 7- <8%	0.94	0.91	0.97
Baseline HbA1c (8-<9%) vs. 7- <8%	0.99	0.95	1.02
Baseline HbA1c (< 7%) vs. 7- <8%	1.13	1.10	1.17
Baseline HbA1c (Miss) vs. 8- <9%	1.01	0.99	1.04

Abbreviations: NonDMDMeds, number of non-diabetes medication classes; BMI, Body mass index; Wt, Weight

*Non-persistence defined as 60 or more days of treatment gap.

**BMI groups: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 5.1 Characteristics of veterans who failed index diabetes treatment following initiation of treatment with oral mono-therapy in FY2000-02 (N=24,872)

	CCIGs					
	None	**Concordant**	**Discordant**	**Both Conc_Disc**	**Dominant**	**All**
	7,437	**3,070**	**7,355**	**4,361**	**2,649**	**24,872**
	29.90%	**12.34%**	**29.57%**	**17.53%**	**10.65%**	**100.00%**
Incident CCIG (1st year)						
None	81.54	86.45	91.19	96.95	100.00	89.67
Concordant	5.62	NA	6.43	NA	NA	3.58
Discordant	9.49	11.04	NA	NA	NA	4.20
Both	1.29	NA	NA	NA	NA	0.39
Dominant	2.06	2.51	2.38	3.05	NA	2.16
Age categories						
Under 55 years	36.49	18.01	50.21	25.91	19.74	34.63
55-64 years	26.81	26.03	26.54	28.89	24.27	26.73
65-74 years	24.90	33.94	16.29	27.63	31.03	24.60
Over 75 years	11.79	22.02	6.96	17.56	24.95	14.04
Gender						
Female	3.03	1.50	4.47	1.88	3.36	3.10
Male	96.97	98.50	95.53	98.12	96.64	96.90
Race/Ethnicity						
White	60.97	77.82	64.99	77.96	74.90	68.70
Black	18.30	13.29	19.42	13.76	15.97	16.97
Other	7.34	4.59	6.80	4.56	6.19	6.23
Miss Race	13.39	4.30	8.80	3.71	2.94	8.10
Marital status						
Married	57.36	61.21	53.13	60.79	57.91	57.25
Not Married	42.06	38.47	46.57	38.96	41.90	42.39
Miss Marital	0.58	0.33	0.30	0.25	0.19	0.37
VHA Priority Code						
Severe Disabled	10.53	11.79	26.09	21.39	24.12	18.64
Mod Disabled	24.15	18.08	25.15	21.97	19.25	22.79
Low Income	43.44	47.23	36.82	43.38	43.41	41.94
Co-Pay	21.33	22.44	11.28	12.89	13.02	16.13
Miss Priority	0.55	0.46	0.65	0.37	0.19	0.50
Non_DMF2F visits						
<= 4	78.63	64.95	49.15	47.12	48.96	59.54
05-8	13.46	16.78	19.97	18.71	15.74	16.96
9-12	4.52	8.37	11.50	11.26	11.36	8.97
> 12	3.39	9.90	19.37	22.91	23.93	14.53

	CCIGs					
	None	**Concordant**	**Discordant**	**Both Conc_Disc**	**Dominant**	**All**
	7,437	**3,070**	**7,355**	**4,361**	**2,649**	**24,872**
	29.90%	**12.34%**	**29.57%**	**17.53%**	**10.65%**	**100.00%**
DMF2F visits						
<= 2	45.81	40.03	37.74	36.78	48.36	41.40
3-4	33.02	32.61	32.92	28.57	25.10	31.32
> 4	21.16	27.36	29.34	34.65	26.54	27.28
PDC categories						
< 0.7	33.16	26.16	32.67	27.20	29.48	30.71
0.7 to < 0.8	14.16	15.47	14.82	16.81	17.78	15.37
0.8 to < 0.9	18.92	23.58	20.95	24.93	24.95	21.79
=> 0.9	33.76	34.79	31.56	31.07	27.78	32.13
Non-DM Meds						
<= 4	65.39	40.26	39.54	27.15	42.24	45.47
5-8	27.16	38.83	35.16	28.92	26.88	31.24
9-12	6.56	17.30	18.30	26.62	19.52	16.26
> 12	0.89	3.62	7.00	17.31	11.36	7.03
Index Rx failure HbA1c						
8 to < 9%	55.64	62.41	57.16	64.18	61.34	59.03
9 to < 10%	22.51	21.92	22.61	20.48	21.74	22.03
=> 10%	21.85	15.67	20.23	15.34	16.91	18.94
Time to index Rx failure						
< 1 year	42.48	33.58	33.35	21.99	17.48	32.43
Between 1-2 years	26.56	24.72	24.42	22.20	19.74	24.21
Between 2-3 years	12.40	15.70	15.27	17.79	15.89	14.97
=>3 years	18.57	25.99	26.96	38.02	46.89	28.39
Rx initiation HbA1c						
< 7 %	8.81	11.01	12.26	13.71	14.65	11.58
7 to < 8 %	16.24	19.35	18.12	21.10	20.84	18.52
8 to < 9%	14.58	16.12	14.85	15.50	13.85	14.93
=> 9%	28.39	22.31	25.60	19.28	20.05	24.33
Miss BslA1c	31.99	31.21	29.16	30.41	30.62	30.63
BMI						
Under/Normal Wt (< 25)	8.73	11.34	7.99	9.54	19.10	10.08
Over Wt (25 to < 30)	31.48	34.50	28.12	30.52	36.28	31.20
Obese (30 to <35)	32.41	30.39	32.15	31.05	26.50	31.22
Morbid Obese (=> 35)	26.18	22.57	31.27	28.09	17.03	26.60
Miss BMI	1.21	1.21	0.46	0.80	1.09	0.90

Abbreviations: CCIGs, Chronic comorbid illness groups; NA, Not Applicable; VHA, Veterans Health Administration; Non_DMF2F, Non diabetes-related face-to-face; DMF2F, Diabetes-related face-to-face; PDC, Proportion of days covered; Non-DM Meds; Non-diabetes medication classes; Rx; treatment; BMI, Body mass index; Wt, Weight

Table 5.2 Type of chronic comorbidity and diabetes treatment intensification in first year following index treatment failure* (N=24,872)

	Diabetes treatment intensification (in %)		
Chronic comorbid illness groups (CCIG)	No Intensification	Intensified to Dual Oral	Intensified to Insulin
None	59.27	39.59	1.14
Concordant	61.37	36.84	1.79
Discordant	52.41	46.13	1.45
Both Conc_Disc	54.83	42.70	2.48
Dominant	61.00	35.52	3.47
Total	56.91	41.30	1.80

*Index diabetes treatment failure was defined as first HbA1c >8% while still on index treatment for 3 or more months following treatment initiation.

Table 5.3 Relationship between type of chronic comorbidity and diabetes treatment intensification in first year following index treatment failure* (N=28,472)

	Outcome: Intensification (Yes vs. No)	
	Unadjusted OR (95% CI)	**Adjusted OR (95% CI) ****
CCIG (ref: None)	1.00	1.00
Concordant	**0.92 (0.84-1.00)**	0.90 (0.82-0.99)
Discordant	**1.32 (1.24-1.41)**	1.06 (0.99-1.14)
Both Conc_Disc	**1.20 (1.11-1.29)**	0.99 (0.91-1.08)
Dominant	0.93 (0.85-1.02)	0.90 (0.82-0.99)

* Index diabetes treatment failure was defined as first HbA1c >8% while still on index treatment for 3 or more months following treatment initiation.

**Adjusted for age groups, race/ethnicity, diabetes-related face-to-face visits, proportion of days covered (PDC), number of non-diabetes medication classes, HbA1c at index failure, time to index treatment failure, and body mass index (BMI).

Table 5.4 Results from final model examining the relationship between type of chronic comorbidity and diabetes treatment intensification in first year following index treatment failure* (N=28,472)

Adjusted Odds Ratios			
		95%	
	OR	Confidence Limits	
Concordant vs. None	0.90	0.82	0.99
Discordant vs. None	1.06	0.99	1.14
Both Conc_Disc vs. None	0.99	0.91	1.08
Dominant vs. None	0.90	0.82	0.995
55-64 vs. Under 55 years	0.92	0.86	0.98
65-74 vs. Under 55 years	0.73	0.68	0.79
Over 75 vs. Under 55 years	0.49	0.45	0.54
Black vs. White	0.76	0.70	0.81
Missing Race vs. White	0.95	0.86	1.05
Other vs. White	1.05	0.94	1.17
DMF2F visits > 4 vs. <= 2	2.18	2.03	2.34
DMF2F visits 3-4 vs. <= 2	1.56	1.46	1.66
PDC (0.7 - <0.8) vs. > 0.9	0.99	0.91	1.08
PDC (0.8-0.9) vs. > 0.9	1.06	0.98	1.14
PDC (<0.7) vs. > 0.9	0.80	0.75	0.86
Non-DM Meds >12 vs. <= 4	1.38	1.23	1.54
Non-DM Meds 9-12 vs. <= 4	1.29	1.19	1.40
Non-DM Meds 5-8 vs. <= 4	1.27	1.19	1.35
Failure HbA1c (=>10%) vs. 8- <9%	1.89	1.76	2.02
Failure HbA1c (9-<10%) vs. 8- <9%	1.45	1.36	1.55
Time to index treatment failure (in years)	1.06	0.98	1.14
1 to <2 vs. < 1			
2 to < 3 vs. < 1	1.19	1.09	1.29
=> 3 vs. < 1	1.69	1.56	1.82
Over Wt vs. Under/Normal Wt*	0.96	0.87	1.05
Obese vs. Under/Normal Wt	1.13	1.03	1.25
Morbid Obese vs. Under/Normal Wt	1.27	1.15	1.41
Miss BMI vs. Under/Normal Wt	0.50	0.35	0.69

Abbreviations: F2F, Face-to-face; DMF2F, Diabetes-related face-to-face; BMI, Body mass index; PDC, Proportion of days covered; Non-DM Meds, number of non-diabetes medication classes; Wt, Weight.
*Defined as first HbA1c >8% while still on index treatment for 3 or more months following treatment initiation.
**BMI groups: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 5.5 Treatment intensification study sensitivity analyses: Restricting analyses to those who survived beyond the first year following index treatment failure (N=23,172)

	Adjusted odds ratios		
	OR	95% Confidence Limits	
Concordant vs. None	0.89	0.81	0.98
Discordant vs. None	1.04	0.97	1.12
Both Conc_Disc vs. None	0.99	0.91	1.08
Dominant vs. None	0.92	0.83	1.02
55-64 vs. Under 55 years	0.93	0.86	0.99
65-74 vs. Under 55 years	0.73	0.68	0.79
Over 75 vs. Under 55 years	0.50	0.45	0.55
Black vs. White	0.75	0.70	0.81
Missing Race vs. White	0.95	0.86	1.06
Other vs. White	1.05	0.94	1.18
DMF2F visits > 4 vs. <= 2	1.98	1.84	2.12
DMF2F visits 3-4 vs. <= 2	1.42	1.32	1.52
PDC (0.7 - <0.8) vs. > 0.9	0.97	0.89	1.05
PDC (0.8-0.9) vs. > 0.9	1.03	0.96	1.11
PDC (<0.7) vs. > 0.9	0.79	0.73	0.85
Non-DM Meds >12 vs. <= 4	1.29	1.15	1.45
Non-DM Meds 9-12 vs. <= 4	1.21	1.12	1.32
Non-DM Meds 5-8 vs. <= 4	1.19	1.12	1.27
Failure HbA1c (=>10%) vs. 8- <9%	1.92	1.79	2.06
Failure HbA1c (9-<10%) vs. 8- <9%	1.46	1.37	1.56
Time to index treatment failure (in years)	1.06	0.99	1.14
1 to <2 vs. < 1			
2 to < 3 vs. < 1	1.18	1.08	1.29
=> 3 vs. < 1	1.68	1.55	1.82
Over Wt vs. Under/Normal Wt*	0.96	0.86	1.06
Obese vs. Under/Normal Wt	1.14	1.03	1.26
Morbid Obese vs. Under/Normal Wt	1.27	1.14	1.41
Miss BMI vs. Under/Normal Wt	0.89	0.58	1.35

Abbreviations: F2F, Face-to-face; DMF2F, Diabetes-related face-to-face; BMI, Body mass index; PDC, Proportion of days covered; Non-DM Meds, number of non-diabetes medication classes; Wt, Weight.
*BMI categories: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 5.6 Treatment intensification study sensitivity analyses: Index treatment failure defined as HbA1c >7% following diabetes treatment initiation (N=44,539)

	Adjusted odds ratios		
	OR	95% Confidence Limits	
Concordant vs. None	0.89	0.83	0.96
Discordant vs. None	0.97	0.91	1.02
Both Conc_Disc vs. None	0.92	0.85	0.99
Dominant vs. None	0.88	0.81	0.97
55-64 vs. Under 55 years	0.82	0.77	0.87
65-74 vs. Under 55 years	0.60	0.57	0.64
Over 75 vs. Under 55 years	0.40	0.37	0.44
Black vs. White	0.73	0.69	0.78
Missing Race vs. White	0.93	0.86	1.02
Other vs. White	1.01	0.92	1.11
DMF2F visits > 4 vs. <= 2	2.45	2.31	2.59
DMF2F visits 3-4 vs. <= 2	1.57	1.49	1.66
PDC (0.7 - <0.8) vs. > 0.9	1.03	0.96	1.11
PDC (0.8-0.9) vs. > 0.9	1.06	0.995	1.13
PDC (<0.7) vs. > 0.9	0.89	0.84	0.95
Non-DM Meds >12 vs. <= 4	1.39	1.27	1.53
Non-DM Meds 9-12 vs. <= 4	1.25	1.17	1.34
Non-DM Meds 5-8 vs. <= 4	1.22	1.16	1.29
Failure HbA1c (=>10%) vs. 8- <9%	2.01	1.84	2.19
Failure HbA1c (9-<10%) vs. 8- <9%	1.50	1.38	1.64
Failure HbA1c (7-<8%) vs. 8- <9%	0.49	0.47	0.52
Time to index treatment failure (in years)	1.02	0.96	1.08
1 to <2 vs. < 1			
2 to < 3 vs. < 1	1.01	0.93	1.08
=> 3 vs. < 1	1.37	1.28	1.47
Over Wt vs. Under/Normal Wt*	1.14	1.05	1.25
Obese vs. Under/Normal Wt	1.26	1.15	1.38
Morbid Obese vs. Under/Normal Wt	1.40	1.28	1.53
Miss BMI vs. Under/Normal Wt	0.84	0.63	1.14

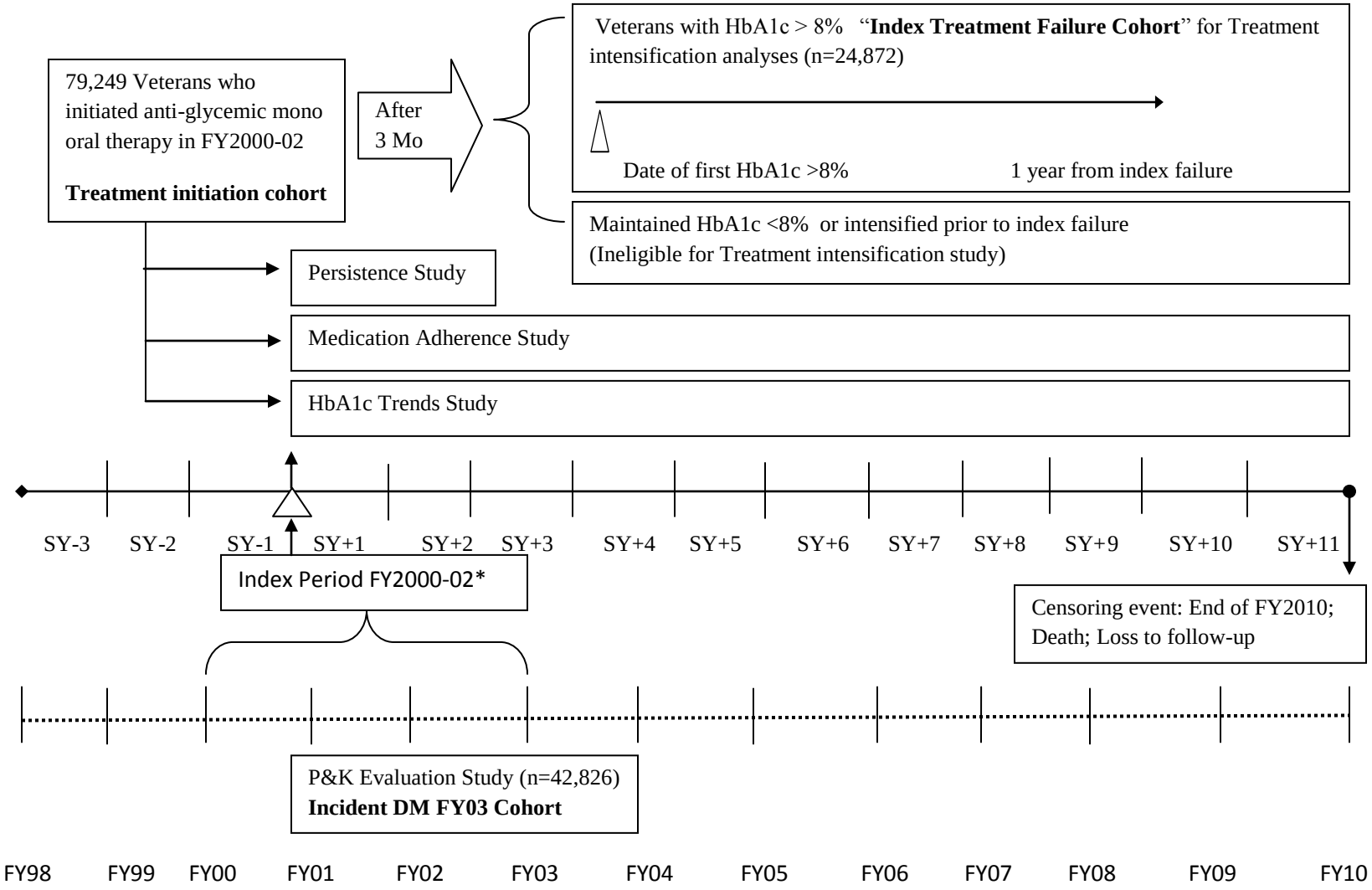
Abbreviations: F2F, Face-to-face; DMF2F, Diabetes-related face-to-face; BMI, Body mass index; PDC, Proportion of days covered; Non-DM Meds, number of non-diabetes medication classes; Wt, Weight.
*BMI categories: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Table 5.7 Treatment intensification study sensitivity analyses: Index treatment failure defined as HbA1c >9% following diabetes treatment initiation (N=13,516)

Adjusted odds ratios			
	OR	95% Confidence Limits	
Concordant vs. None	0.93	0.82	1.05
Discordant vs. None	1.09	0.92	1.20
Both Conc_Disc vs. None	1.05	0.93	1.18
Dominant vs. None	0.99	0.87	1.13
55-64 vs. Under 55 years	0.93	0.85	1.02
65-74 vs. Under 55 years	0.78	0.70	0.86
Over 75 vs. Under 55 years	0.52	0.45	0.59
Black vs. White	0.81	0.74	0.88
Missing Race vs. White	0.95	0.84	1.08
Other vs. White	1.09	0.94	1.25
DMF2F visits > 4 vs. <= 2	2.25	2.05	2.48
DMF2F visits 3-4 vs. <= 2	1.60	1.46	1.75
PDC (0.7 - <0.8) vs. > 0.9	0.93	0.83	1.04
PDC (0.8-0.9) vs. > 0.9	1.06	0.96	1.18
PDC (<0.7) vs. > 0.9	0.72	0.65	0.79
Non-DM Meds >12 vs. <= 4	1.56	1.33	1.82
Non-DM Meds 9-12 vs. <= 4	1.38	1.24	1.55
Non-DM Meds 5-8 vs. <= 4	1.33	1.22	1.45
Failure HbA1c (=>10%) vs. 9- <10%	1.31	1.22	1.41
Time to index treatment failure (in years)	1.11	1.00	1.22
1 to <2 vs. < 1			
2 to < 3 vs. < 1	1.19	1.06	1.34
=> 3 vs. < 1	1.78	1.60	1.98
Over Wt vs. Under/Normal Wt*	0.95	0.84	1.08
Obese vs. Under/Normal Wt	1.07	0.94	1.22
Morbid Obese vs. Under/Normal Wt	1.27	1.11	1.45
Miss BMI vs. Under/Normal Wt	0.61	0.40	0.93

Abbreviations: F2F, Face-to-face; DMF2F, Diabetes-related face-to-face; BMI, Body mass index; PDC, Proportion of days covered; Non-DM Meds, number of non-diabetes medication classes; Wt, Weight.
*BMI categories: Under/Normal Wt (< 25), Over Wt (25 to <30), Obese (30 to <35), Morbid obese (=> 35)

Figure 1.1 Study Schematic



Abbreviations: SY, Study Year; FY, Fiscal Year; P&K, Piette and Kerr; DM, Diabetes Mellitus
*Index event was initiation of anti-glycemic mono oral therapy in FY2000-02

Figure 1.2 Cohort selection flowcharts:

Fig 1.2a Piette and Kerr Evaluation Study Cohort

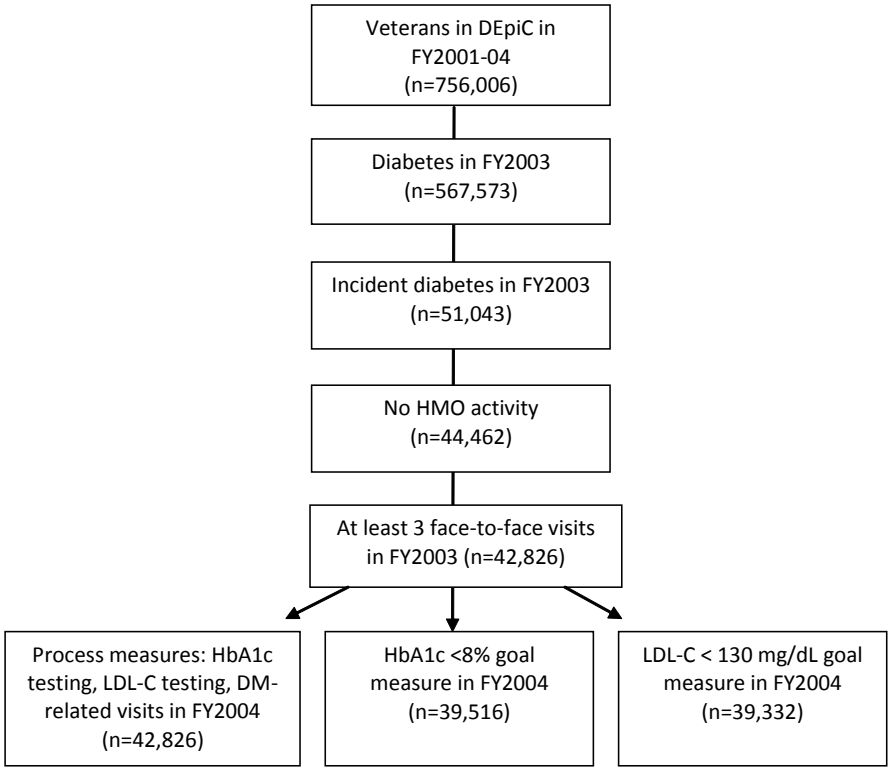


Fig 1.2b Treatment initiation and

Index Treatment Failure Cohorts

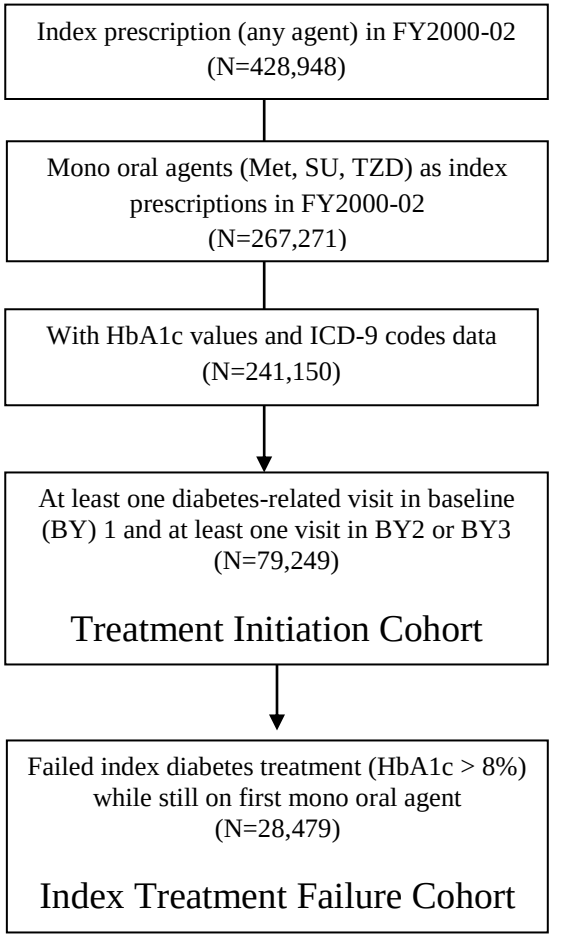


Figure 3.1 Plots of unadjusted quarterly mean HbA1c values by chronic comorbid illness groups

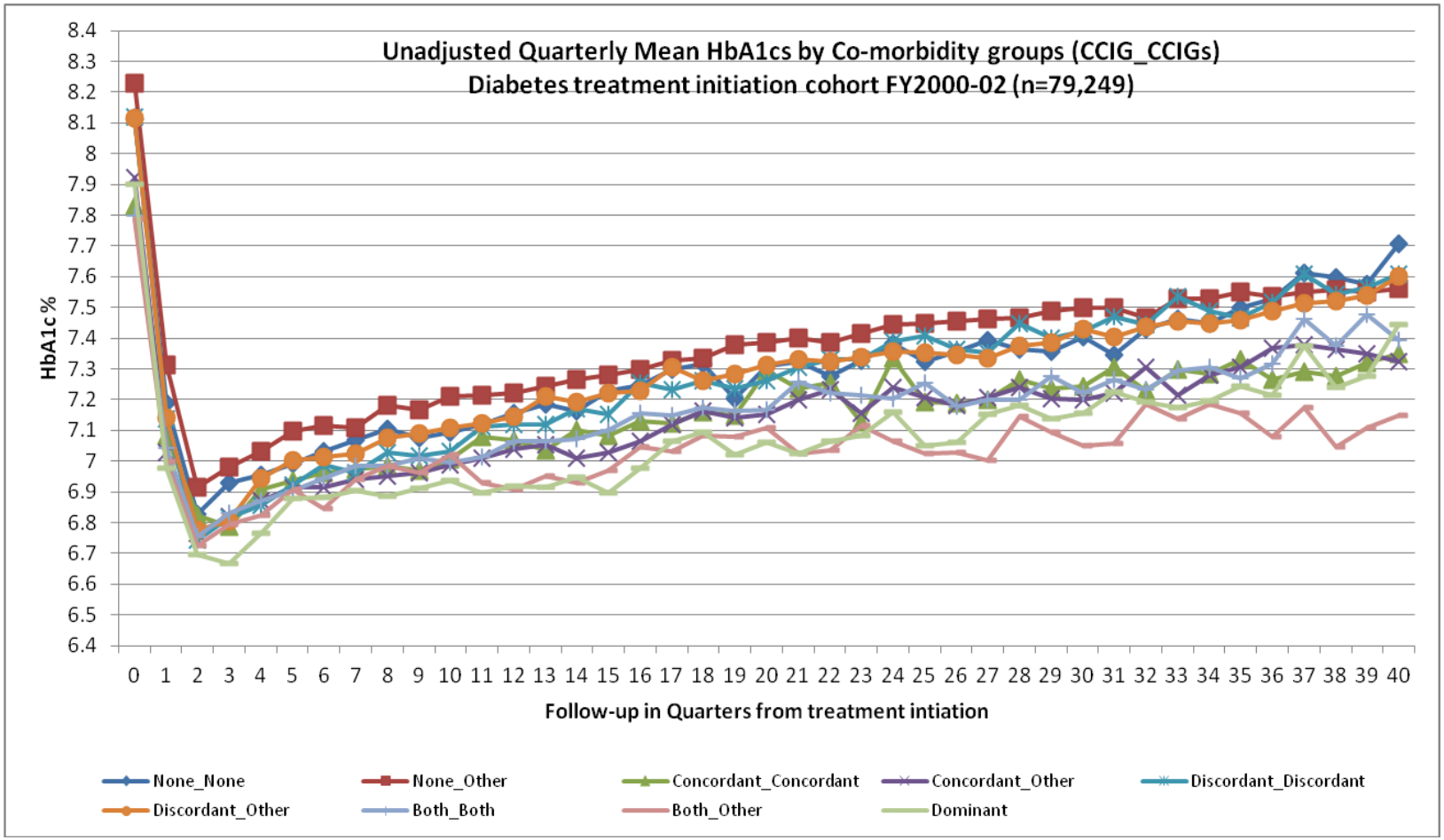
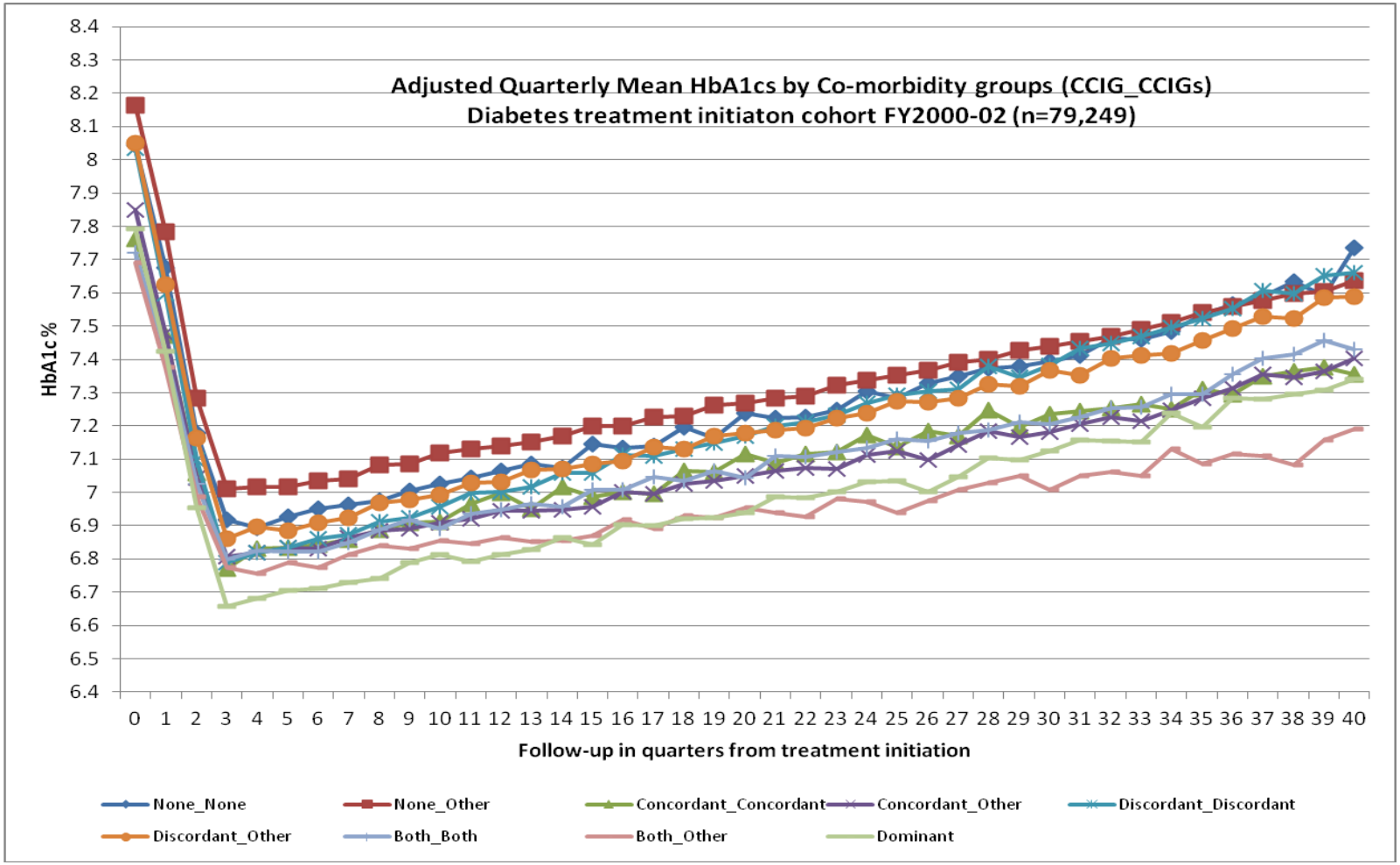


Figure 3.2 Plots of adjusted* quarterly mean HbA1c values by chronic comorbid illness groups using predicted HbA1c values from final piecewise linear random effects model



*Adjusted for age groups, race/ethnicity, marital status, priority status, seasonal variation (sine and cosine terms), baseline HbA1c, baseline body mass index (BMI), annual change in BMI relative to baseline BMI, non diabetes-related face-to-face visits, diabetes-related face-to-face visits, and type of diabetes-medications.

Figure 4.1 Crude survival curve for overall cohort showing persistence with diabetes medications (no treatment gaps of 60 days or more) following treatment initiation

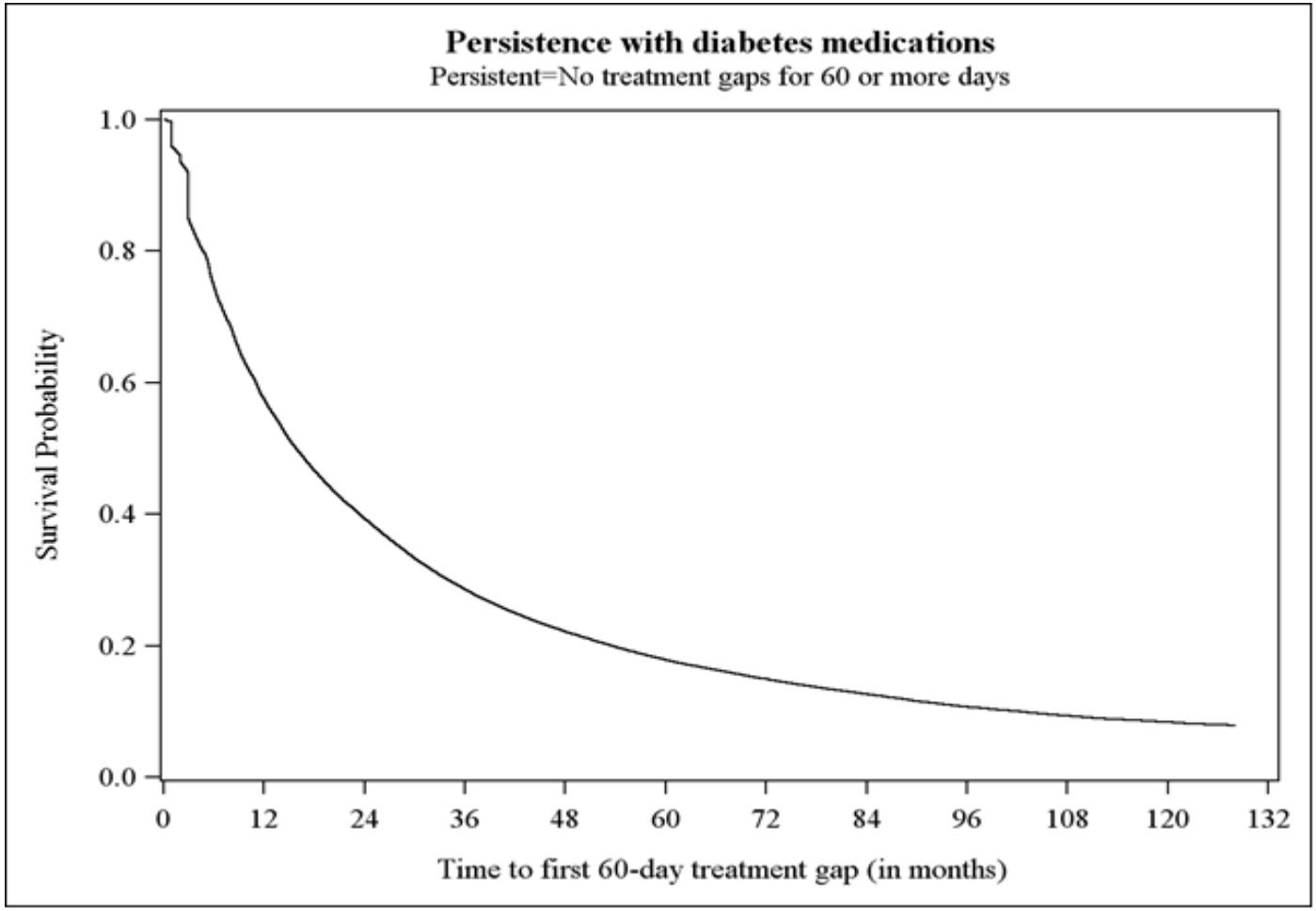


Figure 4.2 Unadjusted survival curves for persistence with diabetes medications (no treatment gaps of 60 days or more), for the first 2 years following treatment initiation, by comorbidity groups

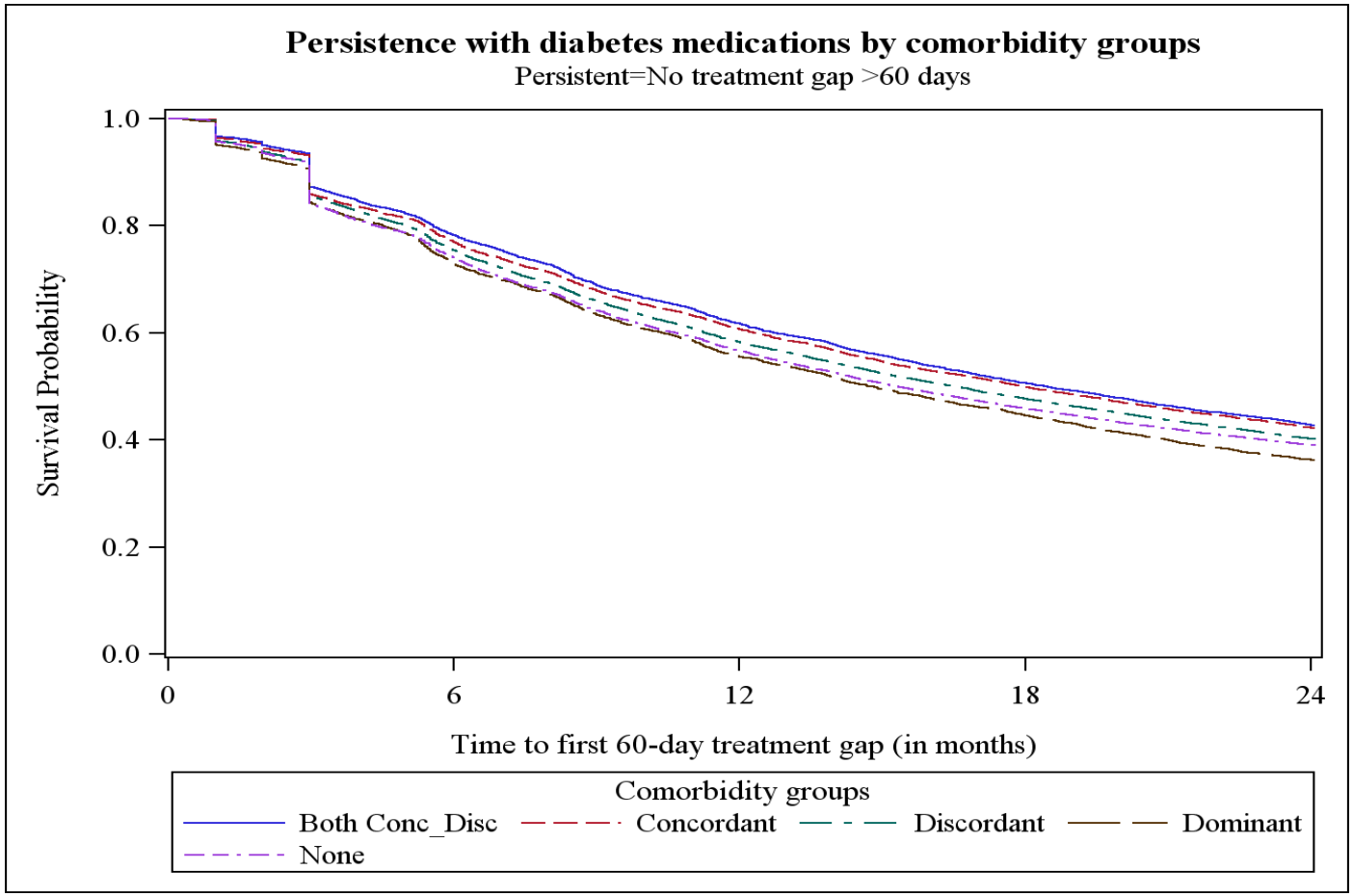
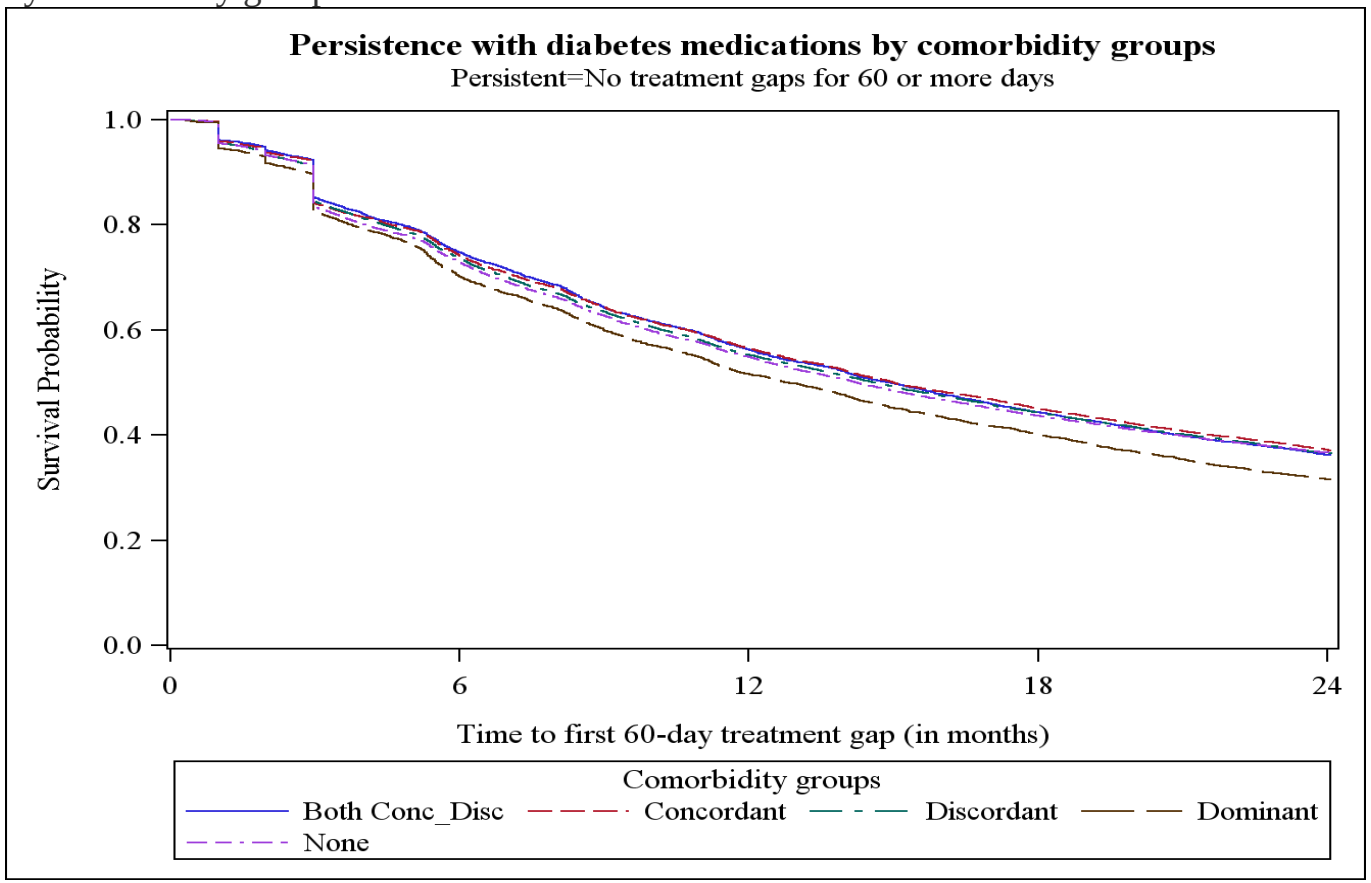


Figure 4.3 Adjusted* survival curves for persistence with diabetes medications (no treatment gaps of 60 days or more), for the first 2 year following treatment initiation, by comorbidity groups



*Adjusted for age categories, race/ethnicity, marital status, Veterans Health Administration (VHA) priority code, incident comorbidity, number of non-diabetes medication classes, body mass index (BMI) category, and HbA1c category.

Appendix:

Appendix1. Code-list of ICD-9-CM and CPT codes used in this study

ICD-9-CM code-list was used to identify and classify veterans with new-onset diabetes into the various chronic comorbid illness groups.

CPT code-list was used to identify face-to-face visits.

Chronic Comorbid Illnesses	**International Classification of Diseases, Ninth revision, Clinical Modification codes (ICD-9-CM)**
Concordant Illnesses	**Illnesses with management plans that have some overlap with the ones for diabetes care**
Macrovascular	
Coronary artery disease (CAD)	410, 410.0, 410.1, 410.2, 410.3, 410.4, 410.5, 410.6, 410.7, 410.8, 410.9, 411, 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 (CHF)	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
Cerebrovascular disease (CVD)	431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.01, 434.11, 434.91, 435, 435.0, 435.1, 435.2, 435.3, 435.8, 435.9, 438, 438.0, 438.1, 438.11, 438.12, 438.2, 438.3, 438.4, 438.5, 438.50, 438.51, 438.52, 438.53, 438.8, 438.81, 438.82, 438.89, 438.9
Peripheral vascular disease (PVD)	250.7, 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, 443.81, 443.89, 443.9, 444.22, 444.81
PVD Gangrene	785.4
Microvascular	
Renal disease	Chronic renal failure (CRF)-403.11, 403.91, 404.12, 404.13, 404.92, 404.93, 585, 586,587 Chronic renal pathophysiology (CRP)-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, 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 (ARF)- 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
Diabetic retinopathy	250.50, 250.51, 250.52, 250.53, 362.0, 362.01, 362.02
Lower extremity complications	681.10, 681.11, 682.7, 700.xx, 707.1, 730.76, 730.77
Discordant Illnesses	**Illnesses with management plans that have minimal overlap with the ones for diabetes care**
Gastrointestinal (GI)	
Upper GI	GERD/esophagitis - 530.1x, 530.2x, 530.3x, 530.81 GI & Peptic ulcer- 531.xx, 532.xx, 533.xx, 534.xx
Lower GI	Inflammatory Bowel disease- 555.xx, 556.xx Diverticulitis- 562.11, 562.13
Hepatic/Biliary	Gall bladder and gall stones- 574.xx, 575.xx, 576.xx Viral hepatitis-070.xx
Pulmonary	Chronic pulmonary disorders- 490.xx, 491.xx, 492.xx, 493.xx, 495.xx, 496.xx, 500.xx, 501.xx, 502.xx, 503.xx, 504.xx, 505.xx, 506.4
Musculoskeletal	Gout- 274.xx, 712.xx Hip problems- 719.05, 719.15, 719.25, 719.35, 719.45, 719.55, 719.65,719.75, 719.85, 719.95, 726.5, 733.14, 733.15, 733.42, 820.xx Low back pain- 720.xx, 721.3x, 721.42, 722.10, 722.52, 722.73, 722.83, 722.93, 724.02, 724.2x, 724.3x, 724.4x, 724.5x, 724.6x, 724.7x, 724.8x, 724.9x Osteoarthritis- 715.xx Other arthritis- 716.xx Rheumatoid arthritis- 714.xx Connective tissue disorders rheumatological- 710.0x, 710.1x, 710.4x, 725.xx
Neurological	Multiple Sclerosis- 340.xx Parkinsons- 332.xx Hemiplegia/hemiparesis and paraplegia- 342.xx, 343.1x, 344.1x Muscular dystrophy–359.xx Spinal cord injury- 344.00, 344.01, 344.02, 344.03, 344.04, 344.09, 806.00, 806.01, 806.02, 806.03, 806.04, 806.05, 806.06, 806.07, 806.08, 806.09, 806.1, 952.0 Epilepsy- 345.xx Gastroparesis- 536.3x
Mental illness & substance abuse	
Mental Illness (major)	Schizophrenia –295.xx Bipolar- 296.0, 296.1, 296.4, 296.5, 296.6, 296.7, 296.8, 296.9 Depression- 296.2x, 296.3x Other psychosis- 297.xx, 298.xx, 299.xx PTSD- 309.81
Mental Illness (other)	Anxiety- 300.0x, 300.2x, 300.3x Other Depression- 311, 300.4x
Substance abuse	Alcohol abuse- 303.xx, 305.0x Abuse of other drugs –304.9x, 305.2x, 305.3x, 305.4x, 305.5x, 305.6x, 305.7x, 305.8x, 305.9x

Other	369.6x, 369.7x, 369.8x, 369.9x, 042
Dominant illnesses	**Illnesses with management plans that eclipse the ones for diabetes care**
End-stage hepatic disease	456.0, 456.1, 456.2, 456.20, 456.21, 572.2, 572.3, 572.4, 572.8, 571.xx
End-stage renal disease (including dialysis)	E8791, V451, V56, V560, V568, V5631, V5632, 38.95, 39.27, 39.42, 39.43, 39.95, 54.98 (ICD9-P)
Cancer (excludes 'Other malignant skin cancers' and malignant cancer of prostate)	140.xx, 141.xx, 142.xx, 143.xx, 144.xx, 145.xx, 146.xx, 147.xx, 148.xx, 149.xx, 150.xx, 151.xx, 152.xx, 153.xx, 154.xx, 155.xx, 156.xx, 157.xx, 158.xx, 159.xx, 160.xx, 161.xx, 162.xx, 163.xx, 164.xx, 165.xx, 166.xx, 167.xx, 168.xx, 169.xx, 170.xx, 171.xx, 172.xx, 174.xx, 175.xx, 176.xx, 177.xx, 178.xx, 179.xx, 180.xx, 181.xx, 182.xx, 183.xx, 184.xx, 186.xx, 187.xx, 188.xx, 189.xx, 190.xx, 191.xx, 192.xx, 193.xx, 194.xx, 195.xx, 196.xx, 197.xx, 198.xx, 199.xx, 200.xx, 201.xx, 202.xx, 203.xx, 204.xx, 205.xx, 206.xx, 207.xx, 208.xx
Amputations	84.11, 84.12, 84.13, 84.14, 84.15, 84.16, 84.17, 84.18, 84.19 (ICD9-P)
Advanced retinopathy	362.02, 369.0x, 369.1x, 369.2x, 369.3x, 369.4x
Dementia	290.0x, 290.10, 290.11, 290.12, 290.13, 290.2x, 290.21, 290.3, 290.40, 290.41, 290.42, 290.43, 291.2x, 294.10, 294.11, 294.8x, 331.0x, 331.1x, 331.2x, 331.7x, 331.89, 331.9x, 331.82, 332.0x, 046.1x, 046.3x, 094.1x, 292.82, 310.9x
Pre-dementia/ Cognitive impairment	294, 294.1, 292.83, 294.9, 331.83, 780.93, 438.xx, 333.0x, 333.4x, 331.5x
CPT Code-list for	**Current Procedure Terminology (CPT) Code-list to identify face-to-face (F2F) visits**
Total F2F visit	90801, 90802, 90804 - 90819, 90821, 90822, 90823, 90824, 90826, 90827, 90828, 90829, 90845, 90847, 90849, 90853, 90857, 90862, 90870, 90871, 90875, 90876, 92002 - 92014, 99201, 99202, 99203, 99204, 99205, 99211, 99212, 99213, 99214, 99215, 99241, 99242, 99243, 99244, 99245, 99301, 99302, 99303, 99311, 99312, 99313, 99321, 99322, 99323, 99331, 99332, 99333, 99341 - 99350, 99354, 99355, 99384- 99387, 99394 - 99397, 99401, 99402, 99403, 99404, 99411, 99412, 99420, 99429, 99499
Diabetes-related F2F visit	250.xx code in visit with above listed CPT codes