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EFFECT OF HOSPITALIZATION ON THE INTEGRITY OF THE MEDICATION REGIMEN IN PATIENTS WITH DIABETES MELLITUS

BY

MATTHEW J ALCUSKY

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE

IN

PHARMACOEPIDEMIOLOGY AND PHARMACOECONOMICS

UNIVERSITY OF RHODE ISLAND

2014

MASTER OF SCIENCE THESIS

OF

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UNIVERSITY OF RHODE ISLAND
2014

ABSTRACT

Medication errors are common within the United States health system. Preventable medication errors are often the result of ineffective processes that contribute to the occurrence of adverse drug events. Care transitions, movement between settings or levels of care, present a particularly vulnerable time for patients. Errors are frequently introduced into a patient's medication regimen during transitions of care, including the inappropriate discontinuation or duplication of medications. Inappropriate discontinuation (non-persistence) of evidence based therapies for chronic diseases places patients at an increased risk for adverse health outcomes. Previous investigations have indicated that care transitions due to hospitalization have been associated with increased rates of non-persistence, and that non-persistent patients were at an increased risk for poor health outcomes.

We conducted a matched retrospective cohort study of patients enrolled with the commercial health insurer Blue Cross Blue Shield of Rhode Island. Patients included in the study were adults at least 18 years of age with diagnosed diabetes confirmed by outpatient medication use and a diagnosis code. We evaluated the disruptive impact of hospitalization on the medication regimen by comparing the odds of persistence with evidence based therapies between hospitalized and non-hospitalized patients. Persistence was assessed with two medication classes: angiotensin converting enzyme (ACE) inhibitors/angiotensin II receptor blockers (ARBs) and lipid lowering drugs (LLD). We classified patients with an eligible hospitalization as exposed, and matched unexposed non-hospitalized patients to the exposed cohort on the variables age, gender, Charlson comorbidity score and enrollment period. The primary outcomes of persistence and treatment duplication were assessed during the 60 day period following the hospitalized patient's discharge date. Differences in baseline characteristics and the bivariate odds of persistence were assessed between groups for the primary risk factor hospitalization as well as patient demographic and health related variables. We constructed multivariable logistic regression models to measure the effect of hospitalization on persistence with medications from each class while controlling for potential confounders and assessing for interaction terms.

A total of 201 exposed and 199 unexposed ACE inhibitor/ARB users and 202 exposed and 199 unexposed LLD users were evaluated for persistence. After adjusting for potential confounders and an interaction term between hospitalization and cardiovascular disease, hospitalization was found to be a

significant risk factor for non-persistence in patients using ACE inhibitors/ARBs [(Beta coefficient-0.931 [P = 0.0283]). Patients that were hospitalized and had cardiovascular disease had an increased odds of persistence relative to patients that were not hospitalized and had cardiovascular disease (Odds Ratio (OR): 2.052 [95% CI 0.384-10.972)]. Patients that were hospitalized and did not have cardiovascular disease were significantly less likely to persist compared with patients that were not hospitalized and did not have cardiovascular disease (OR: 0.394 [95% CI 0.171-0.906]). The odds of persistence with LLD therapy did not differ between hospitalized patients and non-hospitalized patients (OR: 0.961 [95% CI 0.469-1.972]). The duration of prescription supply for study medication was found to be a confounder of the exposure and outcome relationship for both medication classes. Therapeutic duplication occurred infrequently with both medication classes regardless of exposure status and the low frequencies of duplication observed precluded logistic regression analysis.

Our results implicate hospitalization as a risk factor for non-persistence with medications treating chronic diseases in commercially insured patients with diabetes. Interventions such as medication reconciliation that strive to improve communication during transitions of care and prevent the introduction of errors into the medication regimen should continue to be implemented and evaluated.

ACKNOWLEDGMENTS

I would like to acknowledge and express my sincerest gratitude for the enduring guidance and support that I have been fortunate to receive from my major professor, Dr. Kogut. I would also like to recognize the integral contributions made by Dean Quilliam and Dr. Robbins, who anticipated and recommended aspects of the study design and execution that thoroughly improved the quality of the thesis. I am extremely thankful for the generous dedication of time and knowledge provided by Chuck Wentworth, whose strategic instruction markedly improved my SAS analytic skills. I am extremely satisfied with the expansive and applicable education I have acquired through my experience in the pharmacoepidemiology and pharmacoeconomics program. I must once again express my deepest appreciation for the invaluable direction and training provided by Dr. Willey, Dr. Caffrey, Dean Larrat, Dean Quilliam, and Dr. Kogut throughout the MS program.

PREFACE

The standard format was used in preparation of this thesis.

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CHAPTER 1

INTRODUCTION

The conclusions heralded by The Quality of Health Care in America Committee of the Institute of Medicine in their first report "To Err is Human: Building a Safer Health System" called for a system-wide quest for improvement in the quality of healthcare in the United States.[1] In the report, the committee discerned that the majority of medical errors occur as a result of ineffective systems, processes, and conditions that lead individuals to make mistakes or fail to prevent them. In 2006, a successive report "Preventing Medication Errors" evaluated the safe, effective, and appropriate use of medications throughout a multitude of health care settings.[2] The committee estimates that on average a hospitalized patient is subject to at least one medication error per day, and that at least a quarter of all medication-related injuries are preventable. The financial burden of preventable adverse drug events (ADEs) on the United States health care system is substantial. A conservative estimate of $3.5 billion (2006 dollars) is spent annually due to in-hospital preventable ADEs.[2] A care transition is the process of shifting responsibility associated with a patient's movement between settings or level of care.[3] Approximately half of all hospital related medication errors may be attributed to inefficient communications at transitions of care.[4,5]

Transitions of care jeopardize the continued accuracy of a patient's medication regimen.[6-10] Hospitalization places patients at risk for unintentional discontinuation of evidence based therapies for treatment or prevention of chronic diseases.[6,8] Patients undergoing an additional transition to the intensive care unit (ICU) are at a greater risk for discontinuity in chronic medication use.[6-7] The occurrence of unintended medication discrepancies at the time of hospital admission has been estimated to occur in greater than half of patients.[9,10] A prospective study by Cornish and colleagues assessed the accuracy of medication histories for all patients documented to be using at least 4 medications that were admitted from the community to a large teaching hospital in Toronto, Canada.[9] The original medication history was obtained in the emergency department by either a nurse, physician, or medical resident/student. After admission, a pharmacist, pharmacy student or medical student obtained a

thorough medication history which was then compared with the original history. Discrepancies were reviewed with the admitting medical team to appropriately classify intentional and unintentional changes. Of 150 patients included in the study, 81 patients were found to have at least one discrepancy (53.6%; 95% CI 45.7%-61.6%). A total of 140 discrepancies were identified, yielding a rate of 0.93 discrepancies per patient. Of the 140 discrepancies, 8 (5.7%) were classified as severe. A similar study by Gleason et al compared pharmacist obtained medication histories after admission to histories obtained by nursing and physician staff prior to admission.[10] The proportion of patients with at least one medication discrepancy was greater in this study (69% ; 1.2 discrepancies/patient [SD: 1.5]), but discrepancies were not confirmed to be unintentional as in the study by Cornish et al.[9,10]

Inappropriate alteration of the medication regimen upon admission and discharge from the hospital is associated with adverse drug events and poor health outcomes.[7,8] Boockvar et al examined the impact of care transitions on medication use in patients admitted to 2 academic hospitals from 4 different nursing homes.[8] Nursing home and hospital medical records were compared for 87 patients (122 admissions) and reviewed by 2 physicians to identify ADEs attributable to medication changes during transitions of care. A mean of 3.1 medications were altered upon transition from the nursing home to the hospital, which was greater than the 1.4 that were altered upon discharge back to the nursing home ($P<0.001$). Of 71 bidirectional transfers reviewed, ADEs attributable to medication changes occurred during 14 (20%) of these transfers and 7 (50%) of these medication changes were therapy discontinuations. These results suggest that patients are at risk of adverse health outcomes due to inappropriate medication discontinuity following transitions of care between institutions.

Patients admitted to a hospital have been demonstrated to incur higher rates of unintended discontinuations of medications treating chronic diseases as compared to non-hospitalized patients.[6] One population based cohort study evaluated the risk of unintentional discontinuation in patients undergoing 1 or more transitions of care. Patients were required to be continuous users for at least 1 year of at least 1 medication from 5 medication classes: statins, antiplatelets/anticoagulants, levothyroxine, respiratory inhalers, and gastric acid suppressants. Compared with non-hospitalized patients the odds of unintentional discontinuation were increased in hospitalized patients without an ICU stay [(statins: OR 1.33; 95% CI 1.29-1.37), (antiplatelets/anticoagulants: OR 1.86; 95% CI 1.77-

1.97), (levothyroxine: OR 1.18; 95% CI 1.14-1.23), (respiratory inhalers: OR 1.50; 95% CI 1.15-1.97), and (gastric acid suppressants: OR 1.50; 95% CI 1.43-1.56)] and increased further in hospitalized patients with an ICU stay [(statins: OR 1.48; 95% CI 1.39-1.57), (antiplatelets/anticoagulants: OR 2.31; 95% CI 2.07-2.57), (levothyroxine: OR 1.51; 95% CI 1.38-1.66), (respiratory inhalers: OR 1.84; 95% CI 1.10-3.08), and (gastric acid suppressants: OR 1.87; 95% CI 1.71-2.05)]. These results demonstrate the disruptive impact one or more hospitalization related transitions of care may have on appropriate medication use in elderly patients.[6]

National and International Focus on Medication Management During Care Transitions

The Joint Commission is an independent non-profit organization responsible for the accreditation and certification of health care organizations and programs in the United States. The Joint Commission's 2014 Hospital National Patient Safety Goal 03.06.01 specifies the maintenance and communication of accurate patient medication information.[11] Performance elements for this goal emphasize the performance of comprehensive medication reconciliation procedures.[11] The Medicare Prescription Drug, Improvement, and Modernization Act of 2003 included legislation that provided reimbursement under the newly created Medicare Part D for medication therapy management programs.[12] A year later eleven national pharmacy professional organizations collaborated to provide a widely applicable and reimbursable definition of medication therapy management.[13]

Medication reconciliation, a primary component of medication therapy management, was later defined by an expert panel representing the American Pharmacists Association and the American Society of Health System Pharmacists in 2007.[14] An abbreviated version of the joint definition states that medication reconciliation is the comprehensive evaluation of a patient's medication regimen during any change in therapy in an effort to avoid errors or interactions, as well as to observe compliance and adherence patterns. A comparison of existing and previous regimens should occur at every transition in care during which the regimen is modified.[14] The use of pharmacists or other qualified healthcare professionals for medication reconciliation purposes during care transitions presents the potential for limiting medication errors and improving health outcomes.[15-26]

The World Health Organization (WHO) introduced the High 5's project in 2006 as an international initiative responsible for the implementation and evaluation of five standard operating

procedures (SOP) for the improvement of five areas of patient safety.[27] An SOP for medication reconciliation entitled, " Medication Accuracy at Transitions in Care: SOP for Medication Reconciliation" was developed in Canada and is in the process of being implemented and evaluated in the Netherlands. Results reported in 2013 from the use of the SOP in 12 Dutch hospitals indicated a reduction in the proportion of elderly patients with at least one unintentional medication discrepancy upon admission from the emergency department.[28] An intervention consisting of a medication history obtained by a pharmacy technician was associated with a reduced odds of at least one unintentional medication discrepancy [OR 0.29; 95% CI = 0.23-0.37] compared with usual care involving a nurse or physician obtained medication history.[28] Complete results and disclosure of the SOP is planned for 2015.[29]

Adherence and Persistence

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Work Group defines compliance (synonym: adherence) as "the extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen".[30] The ISPOR Work Group defines persistence as "the duration of time from initiation to discontinuation of therapy". Persistence analyses must also include a pre-specified limit on the number of days allowed between refills before a patient is identified as non-persistent.[30] Poor adherence to evidence based therapy has been frequently documented in outpatient populations.[31-32] Non-persistence and sub-optimal adherence prevents the full therapeutic benefit of a drug from being realized and is a cause of preventable adverse health outcomes including mortality.[33-36] Inappropriate medication taking behavior increases resource utilization and the risk of mortality, leading to parallel increases in economic costs and burdens on the health care system.[2, 37-38]

Lipid Lowering and Antihypertensive Therapy in Patients with Diabetes

The prevalence of diagnosed diabetes mellitus has increased steadily from an age adjusted 2.8% of the United States non-institutionalized population in 1980 to 6.4% in 2011.[39] Persons with diabetes mellitus require appropriate lifestyle and medication interventions to mitigate an elevated risk of microvascular and macrovascular complications.[40] Management of dyslipidemia using statin therapy is recommended regardless of baseline lipid levels in patients with cardiovascular disease (CVD) or in

those older than 40 years of age without CVD but that have at least one other CVD risk factor identified.[41] Statin therapy is also recommended in patients that are younger than 40 years of age having multiple CVD risk factors or having a low density lipoprotein (LDL) cholesterol level of greater than 100 mg/dL.[41] The risk of major vascular events and all cause mortality is reduced in patients with diabetes using statin therapy for either primary or secondary prevention.[42-44] In a meta analysis of over 18,000 patients with diabetes from 14 randomized controlled trials, statin therapy was associated with a 9% reduction in all-cause mortality and a 13% proportional reduction in vascular mortality for each millimole per liter reduction in low density lipoprotein (LDL) cholesterol.[43]

Inhibitors of the renin-angiotensin system (RAS) are preferred as initial therapy for hypertension in patients with diabetes due to associated reductions in the occurrence of microvascular and macrovascular outcomes.[40] The HOPE study evaluated the use of the ACE inhibitor ramipril compared with placebo in 3,577 patients with diabetes.[45] Patients were at least 55 years of age and had a history of a prior cardiovascular event or at least one current cardiovascular disease risk factor. The study was stopped before completion due to pronounced beneficial effects in patients receiving ramipril. The combined primary outcome of myocardial infarction, stroke, or cardiovascular death was reduced by 25% (95% CI: 12-36; P=0.0004), total mortality was reduced by 24% (95% CI: 8-37%) and nephropathy was also reduced by 24% (95% CI: 3-40%; P=0.027).[45] The 2014 Standards of Diabetes Care recommend that patients with diabetes and a confirmed blood pressure greater than 140/80 mmHg have prompt initiation and titration of pharmacological antihypertensive therapy. Pharmacological therapy should include either an angiotensin-enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), substituting one class for the other if the first is not tolerated.[40]

Purpose and Hypothesis

The purpose of this study was to investigate the potential disruptive impact that hospitalization may have on medication persistence with critical medication classes used in patients that have diabetes. In patients with confirmed use of at least one of two classes of these evidence based medications, we determined if the prescriptions were renewed in the 60 day period after discharge. Furthermore, we compared the medication discontinuation rate of hospitalized patients to that of matched patients that were not hospitalized. Additionally, we measured the rate of treatment duplication (multiple

prescriptions from the same medication class) between hospitalized and non-hospitalized patients. The effect of time to follow up with a primary care physician on persistence was also examined among patients that were hospitalized.

We expected hospitalization to affect a patient's medication regimen and medication taking behavior due to multiple system related factors. Upon arrival to the hospital, a medication history is obtained by emergency room staff. The completeness and accuracy of medication histories obtained prior to or during the admission process are likely to vary depending upon systemic factors including hospital policies, procedures and staffing models. During the course of a hospitalization, medications treating chronic diseases are often suspended and new medications are added in the course of managing the acute inpatient episode. Substitution of hospital formulary medications will also occur for non-formulary drugs that a patient uses at home. As a patient is prepared for discharge, new medications added during the hospitalization may be continued and chronic medications may be resumed depending upon the patient's condition. Hospital formulary drugs should be changed back to the patient's original medication used prior to admission. Effective communication between hospital practitioners, the patient and/or caregiver, and outpatient practitioners is necessary to reduce the risk for introduction of errors into the medication regimen.

A patient's medication taking behavior, encompassing adherence and persistence with prescribed therapies, is expected to be impacted by a hospitalization. The Necessity Concerns Framework proposes that patient perceptions of their own need for treatment and the potential for adverse consequences related to treatment are the main categories of beliefs that influence patient adherence.[46] Application of this conceptual framework in research studies has shown that adherence increases with parallel increases in perceived necessity of therapy and decreases in concerns regarding the medication.[46] The experience of acute hospitalization may increase a patient's perceived disease severity, therefore increasing the likelihood of adherence after discharge. Alternatively, it is possible that a patient attributes a hospitalization to a lack of effect or adverse consequence of their medication leading to decreased adherence after discharge.

Evidence based medications for which persistence and treatment duplication were assessed in this study consisted of two classes, LLDs and ACE inhibitors/ARBs. ACE inhibitors and ARBs are

used interchangeably in therapy and were regarded as a single class of medications for this study. We hypothesized that hospital admission would increase the likelihood that disruption of a patient's medication regimen would occur, thus causing unintentional discontinuation of evidence based therapies as well as duplications of drug therapy in error. We expected disruption to occur because of the many systematic modifications made to the medication regimen during hospitalization, and due to absent or sub-optimal hospital based medication reconciliation practices. We expected that along with hospitalization, a longer time to follow up with a primary care provider would be associated with a decreased likelihood of persistence due to a longer time until potential resolution of errors introduced into the medication regimen.

CHAPTER 2

METHODOLOGY

The study was conducted as a matched retrospective cohort study of patients with diabetes enrolled with a commercial insurer. The data for this research were provided by Blue Cross Blue Shield of Rhode Island and contained information on enrollment and demographics, as well as pharmacy and medical claims. Patients were at least 18 years of age as of July 1, 2008 and continuously enrolled for at least 12 months between the period of July 1, 2008 to December 31, 2009. All patients were confirmed to have a diagnosis code for diabetes. International classification of diseases ninth edition (ICD-9) codes from the 2009 Healthcare Effectiveness Data and Information Set (HEDIS)[47] were used to identify the presence of any code indicative of diabetes or a diabetes related complication (Appendix A) throughout each patient's period of continuous enrollment. In addition, all patients were confirmed to have used a medication for the treatment of diabetes, defined as the presence of a claim for any oral or injectable hypoglycemic agent during each patient's continuous enrollment period. Patients were identified using unique identification (ID) numbers in the data file; IDs without associated values for date of birth, gender, and eligibility were removed from the study population.

Defining Exposure

The primary outcome of interest in this study was the odds of persistence with chronic medications between hospitalized and non-hospitalized patients. The exposed group in this study consisted of patients hospitalized for at least one night (claims from two consecutive days) and for no greater than 30 days. Patients with multiple hospitalizations during the study period were excluded from the patient population. Current Procedural Terminology (CPT) codes from the 2009 HEDIS (Appendix B)[47] were used to identify acute and non-acute inpatient episodes of care representative of an eligible hospitalization. Coding for emergency department visits was not included in the definition of an eligible hospitalization. Patients with an eligible hospitalization stay were required to have 180 days of continuous enrollment prior to the date of admission and 60 days after the date of hospital discharge. Medication use was evaluated prior to hospital admission with two medication classes (Appendix C),

angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and lipid lowering drugs (LLD). Inclusion into the final cohort of exposed patients required at least two prescription claims for one or more medications within one of these classes during the 180 days prior to hospitalization. Separate analyses were conducted for each medication class, allowing for patients to be included in each analysis group if medications from both classes were used during the baseline period.

Unexposed Matching

Patients without a hospital stay during the study period were unexposed and a source of potential matches for eligible exposed patients. Hospitalized patients were initially linked with all potential matches that consisted of non-hospitalized patients of the same age and gender. Of these potential matches, patients with an enrollment period that encompassed the entire 180 day baseline and 60 day post hospitalization period of the linked exposed patient were retained. Matched patients were assigned an index date identical to the relevant hospitalized patient, with entirely coincident baseline and follow up periods. At least two prescription claims for the same study medication class used by the hospitalized patient were confirmed for potential matches during the 180 day baseline period. The final matching criterion was a comorbidity score calculated using weights as described by Charlson et al and updated ICD-9 codes identified by Quan et al.[48,49] A comorbidity score was calculated for all patients and the distribution of scores was then divided into four groups. Since all patients had previously been confirmed to have a diagnosis of diabetes, the comorbidity score was calculated without diabetes diagnoses. Diabetes related complications were still included in the score calculation. The majority of patients had a minimal comorbid disease burden and the distribution of the comorbidity score was highly skewed (Appendix D). Due to the skewed distribution, the four groups were created as follows: no comorbid disease (score of 0), one comorbid disease (score of 1), patients with two comorbid diseases (score of 2), and three or more comorbid diseases (score of >3). Potential matches with the same comorbidity grouping as the hospitalized patient met all criteria and were eligible to be matched. Matches were assigned to hospitalized patients on a one to one basis without replacement. If a hospitalized patient had multiple eligible matches, a random number was assigned to all potential matches and a final match was assigned at random.

Defining Persistence

Persistence was previously defined by the ISPOR Workgroup as "the duration of time from initiation to discontinuation of therapy".[30] In our study all patients were required to have at least two claims during the baseline period prior to the index hospitalization, and a third claim during the follow up period was indicative of continued use of the medication (persistence). Persistence was evaluated as a dichotomous variable during the 60 day period following the discharge date of the hospitalized and matched patients. Patients without a prescription claim for any medication during this period were excluded from the analysis. Persistence was confirmed if the patient filled a prescription during the 60 day follow up period for any medication within the study drug class of interest. Patients without a claim for such a prescription were classified as non-persistent.

Defining Therapeutic Duplication

Therapeutic duplication was evaluated as a dichotomous variable during the 60 day period following the discharge date of the hospitalized and matched patients. Patients without a prescription claim during the follow up period were excluded from this analysis. Therapy was considered duplicated if claims were identified for greater than one generic medication name within a study drug class (ACE inhibitors/ARBs and LLD) during the post discharge period. Changes in dosing were not captured as therapeutic duplications. To reduce the potential for misclassifying patients using ACE inhibitors/ARBs who were intentionally prescribed multiple medications within the same class, patients confirmed to have been on multiple medications within the same class during the baseline period were excluded. To reduce the potential for misclassifying patients intentionally prescribed multiple LLD, therapeutic duplication was evaluated only for statins. Statins are the most commonly used class of LLD and there is no clinical situation in which duplicating statin therapy is considered appropriate.[41]

Potential Confounding Variables

Age: Parametric assessment of the relationship between the continuous variable age and the dichotomous variable persistence for patients using ACE inhibitors/ARBs depicted a non-linear relationship. Age was coded categorically into three groups for the ACE inhibitor/ARB analysis. Age was determined to have a linear relationship with persistence for patients using lipid lowering drugs, and was coded as a continuous variable.

Gender: Analyzed as a dichotomous variable.

Comorbidity Score Category: The comorbidity score was constructed based upon ICD-9 coding from the 180 day baseline period. This variable was grouped into four categories due to its skewed distribution. The comorbidity score grouping was used as a criteria for matching non-hospitalized patients to hospitalized patients.

Days' Supply: Patients in this study that received prescriptions containing a supply of medication for a period greater than the duration of follow up (60 days) were at risk for misclassification of persistence. Hospitalized patients may have additional medication remaining from a prescription filled prior to hospitalization, and non-hospitalized patients may have filled a prescription for a duration greater than 60 days that is not due for a refill during the follow up period. Duration of prescription supply, in days, was evaluated during the 180 day baseline period and included in the analysis as a dichotomous variable to control for the potential of misclassification.

Individual Comorbid Diseases: The presence of comorbid cardiovascular, respiratory, and mental health disease was identified during the 180 day baseline period using ICD-9 codes from the HEDIS 2009 (Appendix D). The cardiovascular disease variable comprised codes for congestive heart failure, coronary artery disease, myocardial infarction, and other forms of ischemic and non-ischemic cardiovascular disease. Respiratory disease comprised codes for bronchitis, emphysema, and asthma. Mental health disorders included codes for schizophrenia, bipolar disorder, major depression, paranoia, psychosis, anxiety, autism, panic disorder, personality disorders, acute stress disorders, impulse control disorders, anger/aggression disorders, attention deficit disorder, and attention hyperactivity deficit disorder.

Diabetes Medication Regimen: The outpatient diabetes medication regimen was evaluated during the 180 day baseline period and considered a surrogate for severity of disease. This variable was classified categorically into four groups: no outpatient diabetes medication use, monotherapy (no insulin use), polytherapy (no insulin use), and any insulin use.

Medication regimen complexity: Regimen complexity was calculated as the number of unique chemical entities dispensed in the 180 day timeframe preceding the index hospitalization. This variable was determined to have a non-linear relationship with persistence for both medication classes and was coded categorically into four groups based upon quartiles of distribution.

Time Until Primary Care Physician Visit: The time until follow up with a primary care physician was assessed only for hospitalized patients during the 60 day post discharge period and presented as frequencies and percentages.

Statistical Analysis:

Statistical Analysis Software Version 9.3 was used to analyze the data. Patient characteristics of the final matched cohort were stratified by exposure (hospitalization) status and frequency distributions were presented separately for each study medication class in Table 1 (ACE inhibitors/ARBs) and Table 1a (LLD). The Pearson Chi square test was used to assess differences between groups. Continuous variables were compared using t-tests for independent samples or Satterthwaites approximate t-test for variables with unequal variance. The bivariate relationships between hospitalization and persistence, and between other potential confounders and persistence, are presented in Table 2 (ACE inhibitors/ARBs) and table 2a (LLD). Frequencies and percentages of patients persisting were presented for each characteristic as well as the bivariate odds of persistence. Results with a P-value < 0.05 were statistically significant.

Risk factor logistic regression modeling was employed to construct two multivariable models, one each for the matched cohort of patients using ACE inhibitors/ARBs (Table 3a) and the matched cohort of patients using lipid lowering drugs (Table 3b). Hospitalization was the risk factor of interest, with all other independent variables considered potential confounders of the relationship with the dependent variable of persistence. Assessment for collinearity was conducted with all possible confounders for each model. The presence of collinearity was determined based upon identifying a large condition index (>20) with multiple variables associated with a proportion of variance > 0.50. To evaluate if inclusion of interaction terms improved the model fit, the log likelihood test was used to compare models with interaction terms to reduced models. The difference in the –2 log statistic between the full model and the reduced model was compared to the corresponding Chi square statistic with the degrees of freedom equal to the difference in the number of terms in the models. The full model contained all possible two-way interactions, and a backwards elimination process was used to remove the least significant interaction terms at each step. Only interaction terms with a p-value < 0.10 were retained in the final model.

A confounding assessment was performed for all variables. The hospitalization beta estimate for the full model with all variables and retained interaction terms was used as the standard for comparison. The effect each variable had on the hospitalization beta estimate was evaluated by comparing the full model estimate to the estimate from a reduced model containing all items except for the variable being assessed (Appendix E).. Variables that conferred a significant change in the beta estimate when eliminated from the model were identified as confounders that were important for inclusion in the final multivariable model. The final multivariable model for each drug class contained all significant confounders, interaction terms, and other variables deemed clinically important for model inclusion. The c statistic and the Hosmer-Lemeshow goodness of fit test assessed the calibration of the final model (Appendix F).

Therapeutic duplication within each medication class was evaluated and presented as frequencies and percentages. The frequencies and percentages of hospitalized patients persisting as a function of time to follow up with a primary care provider were presented separately (Table 4 and Table 4a). Time to follow up with a primary care provider was dichotomized at the median, which was the same for both hospitalized ACE inhibitor/ARB users and LLD users.

CHAPTER 3

RESULTS

A total of 8,891 patients met all inclusion criteria (Figure1) and were subsequently evaluated for selection into the exposed cohort of hospitalized patients (Figure 2). Of these patients, 270 were confirmed to have had an eligible hospitalization in conjunction with the use of medication from a study drug class prior to admission (207 ACE inhibitors/ARBs and 206 LLD). A total of 7,421 patients without a hospitalization were assessed for matching eligibility with patients in the exposed cohort. An equal number of unique non-hospitalized patients were assigned as matches for the two cohorts of hospitalized patients. After matching was performed, any exposed or unexposed patients without at least one prescription claim in the follow up period were excluded prior to analysis. The final cohort of patients using ACE inhibitors/ARBs that were evaluated for persistence consisted of 201 exposed and 199 unexposed individuals. The final cohort of patients using lipid lowering drugs that were evaluated for persistence consisted of 202 exposed and 199 unexposed individuals.

ACE Inhibitor/ARB Baseline Characteristics

The analytic cohort of ACE inhibitor/ARB users was comprised of 400 patients (Table 1). The exposed and unexposed patients did not differ on the matched variables of age, gender and comorbidity index grouping. The mean (standard deviation [SD]) age of hospitalized patients and non-hospitalized patients was 56.84 [7.82] and 56.86 [7.80], respectively. There was no statistically significant difference in age between groups for each stratum ($P > 0.947$ for all 3 stratum). The majority of the cohort was male, 66.67% of the hospitalized group of patients and 65.83% of the non-hospitalized group ($P=0.859$). The prevalence of respiratory, cardiovascular and mental health disease was significantly different between groups. Patients with respiratory disease made up 13.93% of the hospitalized group and 7.04% of the non-hospitalized group ($P=0.025$). Patients with cardiovascular disease made up 24.38% of the hospitalized group and 14.57% of the non-hospitalized group ($P=0.013$). Patients with mental health disorders made up 16.92% of the hospitalized group and 8.54% of the non-hospitalized group ($P=0.012$). Variability existed between groups with regards to outpatient diabetes medication

regimens used during the baseline period. Of hospitalized patients, 7.46% were using no diabetes medication, 24.38% were using monotherapy without insulin, 39.80% were using polytherapy without insulin, and 28.36% were using insulin alone or in combination with other medications. Of non-hospitalized patients, 5.53% were using no diabetes medication (P=0.433), 38.69% were using monotherapy without insulin (P=0.002), 35.18% were using polytherapy without insulin (P=0.339), and 20.60% were using insulin alone or in combination with other medications (P=0.071). Hospitalized patients utilized a significantly larger mean number of distinct medications (10.79 [4.81]) compared with non-hospitalized patients [(8.66 [4.40]), (P<0.001)]. Finally, 19.10% of unexposed patients had a prescription supply of greater than 60 days compared with 10.45% in the exposed group. Non-hospitalized patients were significantly more likely to have a prescription supply of greater than 60 days (P=0.0147).

Figure 1 Eligibility Flowchart: Application of Inclusion and Exclusion Criteria

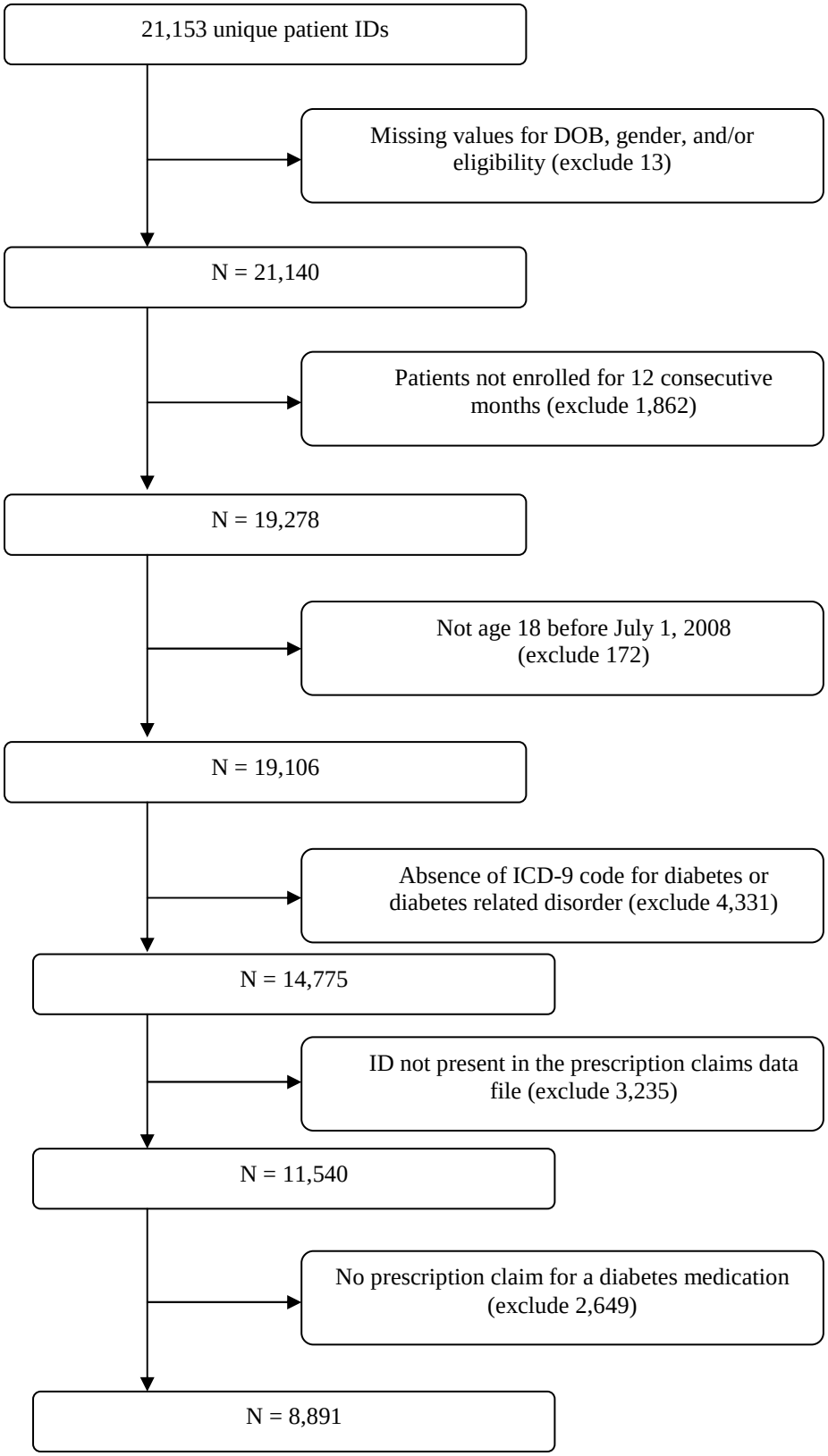

Figure 2 Exposure Classification Flowchart

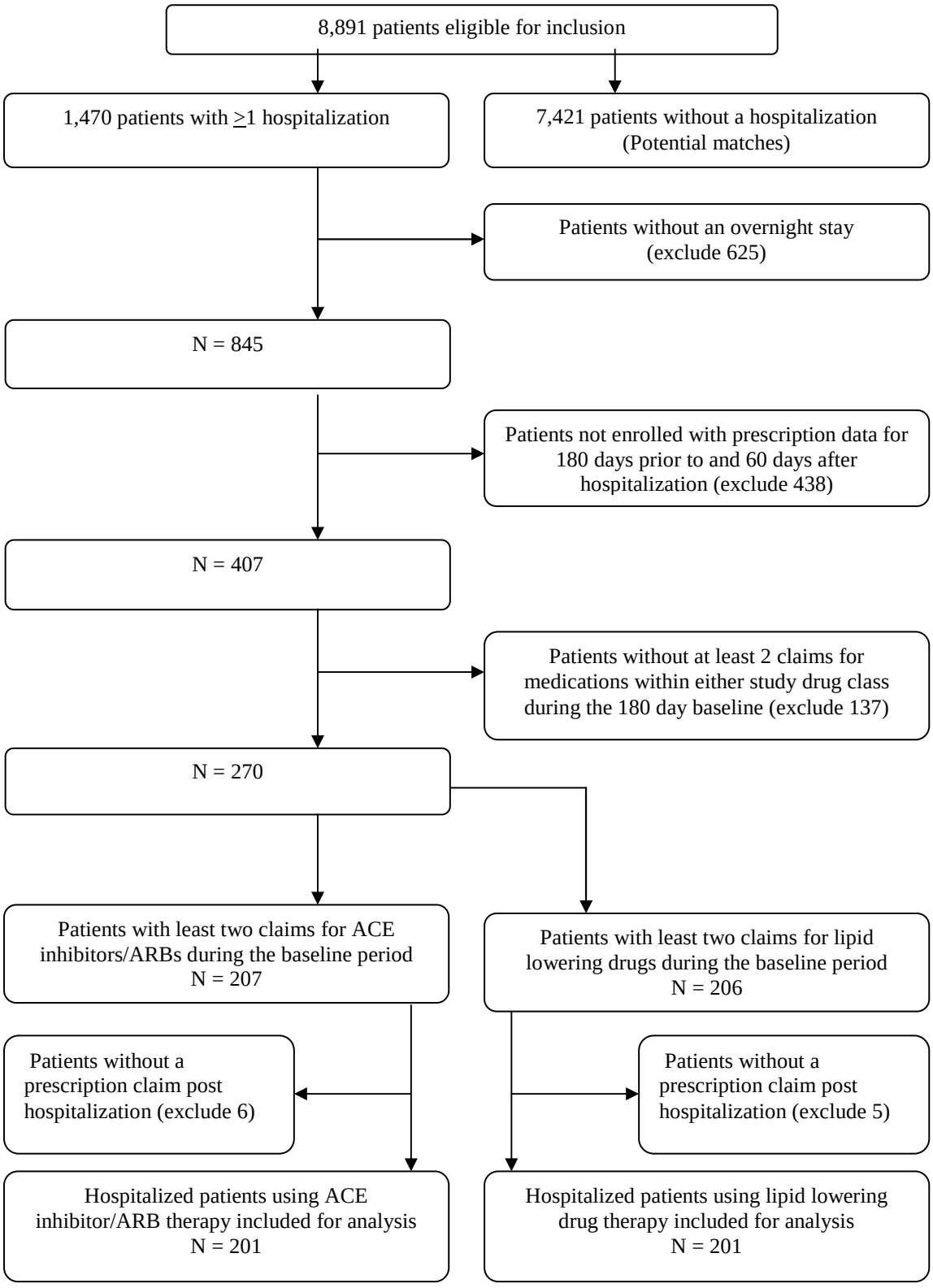

Table 1	**Baseline Characteristics of Hospitalized and Non-hospitalized Patients Using ACE inhibitor/ARB Therapy**		
Characteristic	**Hospitalized (Exposed) N = 201 % (n)**	**Non-Hospitalized (Unexposed) N = 199 % (n)**	**P Value**
Days' Supply	**% (n)**	**% (n)**	**P Value**
≤60 days	89.55 (180)	80.90 (161)	0.0147*
>60 days	10.45 (21)	19.10 (38)	
Age, years	**Mean Age [SD]**		**P Value**
	56.84 [7.82]	56.86 [7.80]	0.981
	% (n)	**% (n)**	**P Value**
Age < 59	53.73 (108)	53.77 (107)	0.994
59 ≤ Age <63	23.88 (48)	24.12 (48)	0.955
63 ≤ Age	22.39 (45)	22.11 (44)	0.947
Gender	**% (n)**	**% (n)**	**P Value**
Male	66.67 (134)	65.83 (131)	0.859
Female	33.33 (67)	34.17 (68)	
Comorbid Diseases	**% (n)**	**% (n)**	**P Value**
Asthma/COPD	13.93 (28)	7.04 (14)	0.025*
Cardiovascular	24.38 (49)	14.57 (29)	0.013*
Mental Health	16.92 (34)	8.54 (17)	0.012*
Diabetes Drug Regimen	**% (n)**	**% (n)**	**P Value**
No Drug Therapy	7.46 (15)	5.53 (11)	0.433
Monotherapy	24.38 (49)	38.69 (77)	0.002*
Polytherapy	39.80 (80)	35.18 (70)	0.339
Any Insulin Use	28.36 (57)	20.60 (41)	0.071
Regimen Complexity	**Mean [SD] Number**		**P Value**
	10.79 [4.81]	8.66 [4.40]	<0.001
	% (n)	**% (n)**	**P Value**
<6 Medications	10.45 (21)	24.12 (48)	<0.001*
6-8 Medications	22.89 (46)	331.7 (66)	0.022*
9-12 Medications	35.82 (72)	27.64 (55)	0.079
12< Medications	30.85 (62)	15.08 (30)	<0.001*
Comorbidity Index[a]	**% (n)**	**% (n)**	**P Value**
No Comorbid Diseases	55.72 (112)	55.28 (110)	0.929
Comorbidity Score = 1	15.92 (32)	15.58 (31)	0.925
Comorbidity Score = 2	15.42 (31)	16.08 (32)	0.857
Comorbidity Score ≥ 3	12.94 (26)	13.07 (26)	0.969

[a] Charlson comorbidity index[48] with updated weighting from Quan et al[49]

* P value is significant. Pearson chi-square test was used for all categorical comparisons and the independent t-test for continuous variables with equal variance or Satterthwaites approximate t-test if variance was unequal

Lipid Lowering Drug Baseline Characteristics

The analytic cohort of lipid lowering drug users was composed of 401 patients (Table 1a). The exposed and unexposed patients did not differ on the matched variables of age, gender and comorbidity index grouping. The mean (standard deviation [SD]) age of hospitalized patients and non-hospitalized patients was 57.16 [7.42] and 57.23 [7.39], respectively (P=0.927). Males made up 66.83% of the hospitalized group of patients and 68.34% of the non-hospitalized group (P=0.747). The prevalence of respiratory and mental health disease was significantly different between groups. Patients with respiratory disease made up 14.85% of the hospitalized group and 7.04% of the non-hospitalized group (P=0.012). Patients with mental health disorders made up 17.33% of the hospitalized group and 8.04% of the non-hospitalized group (P=0.005). Cardiovascular disease was unbalanced between groups but the difference was not statistically significant. Patients with cardiovascular disease made up 26.24% of the hospitalized group and 18.59% of the non-hospitalized group (P=0.067). Significantly more non-hospitalized patients utilized single drug outpatient diabetes regimens, whereas significantly more hospitalized patients utilized regimens involving insulin. Of hospitalized patients, 6.44% were using no diabetes medication, 27.23% were using monotherapy without insulin, 36.63% were using polytherapy without insulin, and 29.70% were using insulin alone or in combination with other medications. Of non-hospitalized patients, 6.03% were using no diabetes medication (P=0.867), 38.69% were using monotherapy without insulin (P=0.145), 35.18% were using polytherapy without insulin (P=0.991), and 18.59% were using insulin alone or in combination with other medications (P=0.009). Hospitalized patients utilized a significantly larger mean number of distinct medications (10.79 [4.54]) compared with non-hospitalized patients [(8.28 [3.73]), (P=0.001)]. Significant differences between groups also existed across all four stratum of the regimen complexity variable. Finally, 15.58% of unexposed patients had a prescription supply of greater than 60 days compared with 9.90% in the exposed group, this difference was not statistically significant (P=0.088).

Table 1a	**Baseline Characteristics of Hospitalized and Non-hospitalized Patients Using Lipid Lowering Drug Therapy**		
Characteristic	**Hospitalized Patients (Exposed) N = 202 % (n)**	**Non-Hospitalized Patients (Unexposed) N = 199 % (n)**	**P Value**
Days' Supply	**% (n)**	**% (n)**	**P Value**
≤60 days	90.10 (182)	84.42 (168)	0.088
>60 days	9.90 (20)	15.58 (31)	
Age, years	**Mean Age [SD]**		**P Value**
	57.16 [7.42]	57.23 [7.39]	0.927
Gender	**% (n)**	**% (n)**	**P Value**
Male	66.83 (135)	68.34 (136)	0.747
Female	33.17 (67)	31.66 (63)	
Comorbid Diseases[c]	**% (n)**	**% (n)**	**P Value**
Asthma/COPD	14.85 (30)	7.04 (14)	0.012*
CVD	26.24 (53)	18.59 (37)	0.067
Mental Health Diagnosis	17.33 (35)	8.04 (16)	0.005*
Diabetes Regimen	**% (n)**	**% (n)**	**P Value**
No Drug Therapy	6.44 (13)	6.03 (12)	0.867
Monotherapy	27.23 (55)	38.69 (77)	0.0145*
Polytherapy	36.63 (74)	36.68 (73)	0.991
Any Insulin Use	29.70 (60)	18.59 (37)	0.009*
Regimen Complexity	**Mean [SD] Number**		**P Value**
	10.79 [4.54]	8.28 [3.73]	<0.001
	% (n)	**% (n)**	**P Value**
<6 Medications	6.93 (14)	23.12 (46)	<0.001*
6-8 Medications	25.25 (51)	35.68 (71)	0.023*
9-12 Medications	38.12 (77)	27.14 (54)	0.019
12< Medications	29.70 (60)	14.07 (28)	<0.001*
Comorbidity Index[a]	**% (n)**	**% (n)**	**P Value**
No Comorbid Diseases	52.97 (107)	53.27 (106)	0.953
Comorbidity Score = 1	11.88 (24)	11.56 (23)	0.920
Comorbidity Score = 2	17.33 (35)	16.58 (33)	0.843
Comorbidity Score ≥ 3	17.82 (36)	18.59 (37)	0.841

[a] Charlson comorbidity index[48] with updated weighting from Quan et al[49]

* P value is significant. Pearson chi-square test was used for all categorical comparisons and the independent t-test for continuous variables with equal variance or Satterthwaites approximate t-test if variance was unequal

Bivariate Odds of Persistence with ACE Inhibitors/ARBs

The bivariate relationship between the dependent variable, persistence with ACE inhibitors/ARBs and all other variables are presented as odds ratios with 95% confidence intervals (OR [95% CI]) (Table 2). Hospitalization, the risk factor of interest, was associated with a decreased likelihood of persistence that did not attain statistical significance (0.733 [0.385 - 1.398]). Patients receiving a prescription supply of greater than 60 days had a significantly decreased odds of persistence with study medication than those with supplies less than 60 days (0.195 [0.098 - 0.392]). The mean (mean [standard deviation]) age of patients that persisted (57.02 [7.81]) was greater than those that did not (55.38 [7.63]). Increasing odds of persistence was observed within each age stratum, but none were significant. Gender was not associated with a change in the likelihood of persistence. Patients with comorbid respiratory disease were slightly more likely to persist (1.589 [0.469 - 5.386]), whereas patients with a comorbid mental health diagnosis were slightly less likely to persist (0.701 [0.293 - 1.673]). Comorbid cardiovascular disease was not associated with a change in the likelihood of persistence. The odds of persistence relative to patients taking no medication for their diabetes was increased in those using single drug therapy (3.091 [0.834 - 11.454]) and in patients using any insulin (1.600 [0.458 - 5.585]) but unchanged in those using multiple drug therapy. The mean number of distinct medications used during the baseline period was not different between persistent (9.718 [4.759]) and non-persistent patients (9.833 [4.509]). Similarly, there were no differences in odds of persistence between the four stratum of regimen complexity. Relative to patients with a comorbidity score of 0, those with a comorbidity score of 1 (1.539 [0.566 - 4.187]) or 2 (1.957 [0.656 - 5.832)] had a non-significantly increased odds of persistence. A comorbidity score of 3 or greater was not associated with a change in the likelihood of persistence.

Table 2 Risk of Non-persistence with ACE Inhibitor/ARB Therapy Post Hospitalization Associated with Patient Demographic and Clinical Characteristics: Bivariate Analyses			
Characteristic	**Persistent (N = 358) % (n)**	**Non-persistent (N = 42) % (n)**	**Odds Ratio (95% CI)**
Not Hospitalized	90.95 (181)	10.05 (18)	Reference
Hospitalized	88.06 (177)	11.94 (24)	0.733 (0.385 - 1.398)
Days' Supply	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
≤60 days	88.27 (316)	59.52 (25)	Reference
>60 days	11.73 (42)	40.48 (17)	0.195* (0.098 - 0.392)
Age, years	**Mean Age [SD]**		**P Value**
	57.022 [7.813]	55.381 [7.635]	0.197
	% (n)	**% (n)**	**Odds Ratio (95% CI)**
Age < 59	57.23 (187)	66.67 (28)	Reference
59 ≤ Age <63	24.58 (88)	19.05 (8)	1.647 (0.721 - 3.761)
63 ≤ Age	23.18 (83)	14.29 (6)	2.071 (0.826 - 5.191)
Gender	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
Male	66.20 (237)	66.67 (28)	Reference
Female	33.80 (121)	3.33 (14)	1.02 (0.518 - 2.011)
Comorbid Diseases[a]	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
Asthma/COPD	10.89 (39)	7.14 (3)	1.589 (0.469 - 5.386)
Cardiovascular	19.55 (70)	19.05 (8)	1.033 (0.458 - 2.329)
Mental Health	12.29 (44)	16.67 (7)	0.701 (0.293 - 1.673)
Diabetes Regimen	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
No Drug Therapy	6.15 (22)	9.52 (4)	Reference
Monotherapy	33.24 (119)	16.67 (7)	3.091 (0.834 - 11.454)
Polytherapy	36.03 (129)	50.00 (21)	1.117 (0.350 - 3.566)
Any Insulin Use	24.58 (88)	23.81 (10)	1.600 (0.458 - 5.585)
Regimen Complexity	**Mean Number [SD]**		**P Value**
	9.718 [4.759]	9.833 [4.509]	0.881
	% (n)	**% (n)**	**Odds Ratio (95% CI)**
<6 Medications	17.04 (61)	19.05 (8)	Reference
6-8 Medications	28.21 (101)	26.19 (11)	0.830 (0.317 - 2.179)
9-12 Medications	32.12 (115)	28.57 (12)	0.796 (0.309 - 2.051)
12< Medications	22.63 (81)	26.19 (11)	1.036 (0.393 - 2.730)
Comorbidity Index[b]	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
CMI Score = 0	54.75 (196)	16.67 (26)	Reference
CMI Score = 1	16.20 (58)	11.90 (5)	1.539 (0.566 - 4.187)
CMI Score = 2	16.48 (59)	9.52 (4)	1.957 (0.656 - 5.832)
CMI Score ≥ 3	12.57 (45)	16.67 (7)	0.853 (0.348 - 2.088)

[a] Reference is the absence of the comorbidity

[b] Charlson comorbidity index[48] with updated weighting from Quan et al[49]

[*] P value is significant. Pearson chi-square tests used for categorical variables and independent t-tests for continuous with equal variance or Satterthwaites approximate t-test if unequal variance

Bivariate Odds of Persistence with Lipid Lowering Drugs

The bivariate relationship between the dependent variable, persistence with lipid lowering drugs, and all other variables are presented as odds ratios with 95% confidence intervals (Table 2a). Hospitalization was not associated with any alteration in the likelihood of persistence (0.918 [0.491 - 1.719]). Patients receiving a prescription supply of greater than 60 days had a significantly decreased odds of persistence with study medication than those with supplies less than 60 days (0.167 [0.083 - 0.337]). The mean (mean [standard deviation]) age of patients that persisted (57.20 [7.25]) was equivalent to those that did not persist (57.16 [8.58]). Gender was not associated with a change in the likelihood of persistence. Patients with comorbid respiratory disease were slightly less likely to persist (0.754 [0.299 - 1.901]). Comorbid mental health or cardiovascular disease were not associated with a change in the likelihood of persistence. The odds of persistence relative to patients taking no medication for their diabetes was increased in those using single drug therapy (2.750 [0.864 - 8.756]), multiple drug therapy (1.912 [0.635 - 5.759]) and in patients using any insulin (1.955 [0.610 - 6.258]). The mean number of distinct medications used during the baseline period was not different between persistent (9.49 [4.40]) and non-persistent patients (9.98 [3.80]). Compared to patients using the fewest number of medications (less than 6) during the baseline period, those in each other stratum of regimen complexity (6-8, 9-12, 12< medications) were more likely to persist. Relative to patients with a comorbidity score of 0, those with a comorbidity score of 1 or 2 had a comparable likelihood of persistence. A comorbidity score of 3 or greater was associated with an increased odds of persistence (1.891 [0.698 - 5.122]).

Table 2a Risk of Non-persistence with Lipid Lowering Drug Therapy Post Hospitalization Associated with Patient Demographic and Clinical Characteristics: Bivariate Analyses			
Characteristic	**Persistent (N = 357) % (n)**	**Non-persistent (N = 44) % (n)**	**Odds Ratio (95% CI)**
Not Hospitalized	89.45 (178)	10.55 (21)	Reference
Hospitalized	89.05 (179)	10.95 (23)	0.918 (0.491 - 1.719)
Days' Supply	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
≤60 days	90.48 (323)	61.36 (27)	Reference
>60 days	9.52 (34)	38.64 (17)	0.167* (0.083 - 0.337)
Age, years	**Mean Age [SD]**		**P Value**
	57.20 [7.25]	57.16 [8.58]	0.978
Gender	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
Male	67.23 (240)	70.45 (31)	Reference
Female	32.77 (117)	29.55 (13)	1.162 (0.586 -2.304)
Comorbid Diseases[a]	**% (n)**	**% (n)**	**Odds Ratio[a] (95% CI)**
Asthma/COPD	10.64 (38)	13.64 (6)	0.754 (0.299 - 1.901)
CVD	22.41 (80)	22.73 (10)	0.982 (0.465 - 2.074)
Mental Health	12.61 (45)	13.64 (6)	0.913 (0.365 - 2.283)
Diabetes Regimen	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
No Drug Therapy	5.60 (20)	11.36 (5)	Reference
Monotherapy	33.89 (121)	25.00 (11)	2.750 (0.864 - 8.756)
Polytherapy	36.41 (130)	38.64 (17)	1.912 (0.635 - 5.759)
Any Insulin Use	24.09 (86)	25.00 (11)	1.955 (0.610 - 6.258)
Regimen Complexity	**Mean Number [SD]**		**P Value**
	9.49 [4.40]	9.98 [3.80]	0.434
	% (n)	**% (n)**	**Odds Ratio (95% CI)**
<6 Medications	15.97 (57)	6.82 (3)	Reference
6-8 Medications	29.97 (107)	34.09 (15)	2.663 (0.740 - 9.582)
9-12 Medications	32.77 (117)	31.82 (14)	2.273 (0.628 - 8.227)
12< Medications	21.29 (76)	27.27 (12)	2.999 (0.809 -11.125)
Comorbidity Index[b]	**% (n)**	**% (n)**	**Odds Ratio (95% CI)**
CMI Score = 0	59.09 (26)	52.38 (187)	Reference
CMI Score = 1	13.64 (6)	11.48 (41)	0.950 (0.367 - 2.456)
CMI Score = 2	15.91 (7)	17.09 (61)	1.212 (0.501 -2.930)
CMI Score ≥ 3	11.36 (5)	19.05 (68)	1.891 (0.698 - 5.122)

[a]Reference is the absence of the comorbidity

[b] Charlson comorbidity index[48] with updated weighting from Quan et al[49]

[*] P value is significant. Pearson chi-square test was used for all categorical comparisons and the independent t-test for continuous variables with equal variance or Satterthwaites approximate t-test if variance was unequal

Multivariable Logistic Regression Model: ACE Inhibitor/ARB Cohort

The results of a multivariable logistic regression analysis of the effect of hospitalization on persistence with ACE inhibitor/ARB therapy, adjusted for relevant confounders and interaction terms, are presented in Table 3. Collinearity was not found between any of the independent variables assessed for inclusion into this model. A single interaction term between the risk factor (hospitalization) and cardiovascular disease met criteria and was included in the final model. After adjusting for all potential confounders and the interaction between hospitalization and cardiovascular disease, the beta coefficient representing the relationship between hospitalization and persistence was significant (-0.931 [P=0.0283]). Due to the inclusion of an interaction term in the model, the odds of persistence in hospitalized patients relative to non-hospitalized patients are presented separately for individuals with and without cardiovascular disease. Patients that were hospitalized and had cardiovascular disease had an increased odds of persistence relative to patients that were not hospitalized that had cardiovascular disease (2.052 [0.384-10.972)]. Patients that were hospitalized and did not have cardiovascular disease were significantly less likely to persist compared with patients that were not hospitalized and did not have cardiovascular disease (0.394 [0.171-0.906]). The only other significant term in the final model was the duration of prescription supply. Patients receiving a prescription supply of greater than 60 days were less likely to have persisted (0.127 [0.056-0.287]) compared with those with a supply of 60 days or less.

Assessment for confounding involved comparison of the beta coefficient and P-value for hospitalization from the final model with the beta coefficient and P-value obtained from a reduced model absent the potential confounder of interest. A substantial change upon variable removal was indicative of confounding. Duration of prescription supply impacted a large magnitude change in the beta coefficient upon removal from the model. Prescription supply was also significantly associated with hospitalization, and as a result was identified as a confounder. Through this same process, the diabetes regimen and medication regimen complexity variables were also identified as confounders. The inclusion of all other variables in the model was determined necessary to adjust for differences in baseline characteristics and due to clinical importance.

Table 3
Influence of Hospitalization on Persistence with ACE Inhibitor/ARB Therapy: Results of a Multivariable Logistic Regression Model

Characteristic	Beta Coefficient	Standard Error	Odds Ratio (95% CI)
Not Hospitalized	-	-	Reference
Hospitalized	-0.931*	0.425	-
Hospitalized (Cardiovascular disease)[a]	-	-	2.052 (0.384 - 10.972)
Hospitalized (No cardiovascular disease)[a]	-	-	0.394* (0.171 - 0.906)
Days' Supply			**Odds Ratio (95% CI)**
≤60 days	-	-	Reference
>60 days	-2.067*	0.418	0.127* (0.056 - 0.287)
Age, years			**Odds Ratio (95% CI)**
Age < 59	-	-	Reference
59 ≤ Age <63	0.580	0.470	1.787 (0.711 - 4.491)
63 ≤ Age	1.000	0.529	2.719 (0.963 - 7.675)
Gender			**Odds Ratio (95% CI)**
Male	-	-	Reference
Female	0.057	0.393	1.058 (0.490 - 2.288)
Comorbid Diseases[b]			**Odds Ratio (95% CI)**
Asthma/COPD	0.570	0.751	1.769 (0.406 - 7.700)
Cardiovascular	-0.936	0.689	-
Cardiovascular (Non-hospitalized)[c]	-	-	0.392 (0.10 - 1.515)
Cardiovascular (Hospitalized)[c]	-	-	2.044 (0.532 - 7.846)
Mental Health	-0.624	-0.624	0.536 (0.191 - 1.507)
Diabetes Regimen			**Odds Ratio (95% CI)**
No Drug Therapy	-	-	Reference
Monotherapy	1.364	0.722	3.912 (0.950 - 16.100)
Polytherapy	0.0572	0.631	1.059 (0.307 - 3.648)
Any Insulin Use	0.693	0.705	1.999 (0.502 - 7.957)
Regimen Complexity			**Odds Ratio (95% CI)**
<6 Medications	-	-	Reference
6-8 Medications	0.785	0.572	2.193 (0.715 - 6.720)
9-12 Medications	0.989	0.567	2.689 (0.885 - 8.163)
12< Medications	1.007	0.642	2.736 (0.777 - 9.637)
Comorbidity Index[d]			**Odds Ratio (95% CI)**
CMI Score = 0	-	-	Reference
CMI Score = 1	0.138	0.598	1.148 (0.356 - 3.704)
CMI Score = 2	0.575	0.591	1.777 (0.558 - 5.661)
CMI Score ≥ 3	-0.572	0.552	0.564 (0.191 - 1.663)

[a] Interaction of hospitalization and cardiovascular disease included in model, odds of persistence for hospitalized relative to non-hospitalized patients reported with and without cardiovascular disease
[b] Reference is the absence of the comorbidity
[c] Odds of persistence for patients with/without cardiovascular disease by hospitalization status
[d] Charlson comorbidity index[48] with updated weighting from Quan et al[49]
* P value is significant at < 0.05

Multivariable Logistic Regression Model: Lipid Lowering Drug Cohort

The results of a multivariable logistic regression analysis of the effect of hospitalization on persistence with lipid lowering drug therapy, adjusted for relevant confounders and interaction terms, are presented in Table 3a. Collinearity was not found between any of the independent variables assessed for inclusion into this model. There were no interaction terms that met criteria for inclusion into the final model. The odds of persistence did not differ between hospitalized patients and non-hospitalized patients (0.961 [0.469-1.972]). Patients receiving a prescription supply of greater than 60 days were much less likely to persist (0.146 [0.068 - 0.313]) relative to patients with a supply of less than or equal to 60 days. Patients utilizing medication to treat diabetes had an increased odds of persistence compared to patients not on drug therapy, regardless of whether it was monotherapy, polytherapy or any regimen containing insulin. The increased odds of persistence achieved statistical significance for patients using monotherapy (3.765 [1.064-13.324]). A consistently lower likelihood of persistence was observed in the three groups of patients with greater regimen complexity (6-8, 9-12, 12< medications) relative to those using 5 medications or less during the baseline period, but this result did not achieve statistical significance.

A confounding assessment was carried out using the process described for the ACE inhibitor/ARB model. Duration of prescription supply caused a large magnitude change in the beta coefficient upon removal from the model. The negative association between prescription supply and hospitalization approached significance (P = 0.088), as a result prescription supply was identified as a confounder. Through this same process, the diabetes regimen and medication regimen complexity variables were both identified as confounders. The inclusion of all other variables in the model was determined necessary to adjust for differences in baseline characteristics and due to clinical importance.

Table 3a
Influence of Hospitalization on Persistence with Lipid Lowering Drug Therapy Adjusted for: Prescription Supply Duration, Age, Gender, Comorbid Disease Burden, Diabetes Medication Regimen and Number of Medications Used
Results of a Multivariable Logistic Regression Model

Characteristic	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
Not Hospitalized	-	-	Reference
Hospitalized	-0.040	0.367	0.961 (0.469 - 1.972)
Days' Supply	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
≤60 days	-	-	Reference
>60 days	-1.926*	0.389	0.146* (0.068 - 0.313)
Age, years	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
Age [a]	0.006	0.024	1.006 (0.959 - 1.055)
Gender	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
Male	-	-	Reference
Female	0.071	0.380	1.074 (0.509 - 2.262)
Comorbid Diseases[b]	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
Asthma/COPD	-0.527	0.617	0.591 (0.176 - 1.977)
Cardiovascular	-0.018	0.437	0.982 (0.417 - 2.312)
Mental Health	0.079	0.535	1.082 (0.379 - 3.086)
Diabetes Regimen	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
No Drug Therapy	-	-	Reference
Monotherapy	1.326*	0.645	3.765* (1.064 - 13.324)
Polytherapy	1.121	0.623	3.068 (0.907 - 10.378)
Any Insulin Use	1.199	0.678	3.316 (0.878 - 12.520)
Regimen Complexity	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
<6 Medications	-	-	Reference
6-8 Medications	-1.205	0.694	0.299 (0.077 - 1.167)
9-12 Medications	-1.071	0.712	0.343 (0.085 - 1.382)
12< Medications	-1.279	0.770	0.278 (0.062 - 1.259)
Comorbidity Index[c]	**Beta Coefficient**	**Standard Error**	**Odds Ratio (95% CI)**
CMI Score = 0	-	-	Reference
CMI Score = 1	0.417	0.615	1.517 (0.454 - 5.064)
CMI Score = 2	0.495	0.505	1.640 (0.610 - 4.412)
CMI Score ≥ 3	0.917	0.601	2.501 (0.770 - 8.129)

[a] Age variable coded as continuous
[b] Reference is the absence of the comorbidity
[c] Charlson comorbidity index[48] with updated weighting from Quan et al[49]
* P value is significant

Therapeutic Duplication

Therapeutic duplication occurred infrequently with both medication classes regardless of exposure status. Of the 189 hospitalized patients that were only using a single ACE inhibitor or ARB during the baseline period, 3 (1.59%) duplicated therapy during the post-hospitalization period. Similarly, of the 186 non-hospitalized patients that were using a single drug during the baseline period, 1 patient (0.54%) duplicated therapy during the follow-up period. Of the 186 hospitalized patients that had 2 or more claims for a statin during the baseline period, 1 patient (0.54%) duplicated therapy. A total of 3 (1.63%) non-hospitalized patients duplicated statin therapy of the 184 that had 2 or more claims for a statin during the baseline period.

Time to Primary Care Physician Visit

The number of patients persisting was similar between patients with a shorter (<12 days) time until a follow up visit with a primary care provider compared with patients with a longer (12≤ days) time until follow up for both ACE inhibitors/ARBS (P=0.537) and for LLDs (P=0.786) (Table 4 and Table 4a).

Table 4 **Influence of Time to Follow Up with a Primary Care Provider on Post Discharge Persistence in Hospitalized Patients Using ACE Inhibitors/ARBs**			
Time Until Follow Up[a]	**Persistent N = 97 % (n)**	**Non-Persistent N = 104 % (n)**	**P Value**
<12 days	47.46 (84)	54.17 (13)	0.537
12≤ days	52.54 (93)	45.83 (11)	

[a] The median time until follow up with a primary care physician was 12 days; 19 patients did not follow up within the 60 day period and were grouped with the patients that had a time until follow up of 12≤ days

Table 4a	**Influence of Time to Follow Up with a Primary Care Provider on Post Discharge Persistence in Hospitalized Patients Using Lipid Lowering Drug Therapy**		
Time Until Follow Up[a]	**Persistent N = 179 % (n)**	**Non-Persistent N = 23 % (n)**	**P Value**
<12 days	50.84 (91)	47.83 (11)	0.786
12≤ days	49.16 (88)	52.17 (12)	

[a] The median time until follow up with a primary care physician was 12 days; 19 patients did not follow up within the 60 day period and were grouped with the patients that had a time until follow up of 12≤ days

CHAPTER 4

DISCUSSION

Transitions of care present a particularly vulnerable time for patients. Inadequate communication both between providers and with the patient has the potential to introduce inaccuracies into the medication regimen and precipitate inappropriate medication taking behavior. Consequent adverse drug events are often preventable, and contribute to increased healthcare utilization and expenditures. The IOM report "Preventing Medication Errors" emphasized transitions of care as an area that requires substantial research to better understand and address the incidence of medication errors.[2] Institutions, clinicians and professional organizations, amongst others, have since mobilized in an effort to determine what patient populations are at the greatest risk and what interventions are most effective for improving patient safety.

The present study investigated the potential of hospitalization to disrupt continuity of appropriate medication use by comparing persistence with evidence based chronic medications between hospitalized and non-hospitalized patients with diabetes. An increased likelihood of inappropriate discontinuation was hypothesized for hospitalized patients using medications within both classes studied, ACE inhibitors/ARBs and LLDs. The effect of hospitalization on persistence [Beta estimate (P-value)] was not consistent between these two medication classes, as hospitalization was a significant risk factor for non-persistence with ACE inhibitors/ARBs [-0.931 (P=0.028)] but there was no effect on the odds of persistence with LLDs [-0.036 (P=0.922)]. The significant negative effect of the risk factor of interest on the odds of ACE inhibitor/ARB persistence [Odds ratio (95% CI)] was modified by the presence [2.052 (0.384-10.972)] or absence [0.394 (0.171-0.906)] of cardiovascular disease. Without inclusion of the interaction between hospitalization and cardiovascular disease in the multivariable model, hospitalization was no longer a significant risk factor for non-persistence (Appendix F). The bivariate models for each medication class supported the lack of association between hospitalization and LLD persistence [0.918 (0.491-1.719)] and the mitigated relationship between hospitalization and ACE inhibitor/ARB persistence [0.733 (0.385-1.398)].

We also investigated hospitalization as a possible risk factor for inappropriate duplication of therapy with both classes of study medications. The low frequencies of duplication observed [(ACE inhibitor/ARB:1.59% hospitalized, 0.54% non-hospitalized); (LLD: 0.54% hospitalized, 1.63% non-hospitalized)] precluded bivariate and multivariable analysis for this outcome. Therapeutic duplication was found to be infrequent in this population due to a confluence of factors. To reduce the likelihood of misclassification, duplication was only assessed for statins as a subclass of the broader class of LLD. The use of multiple LLDs may be therapeutically indicated, whereas the use of more than 1 statin is not appropriate in any clinical situation. Similarly, patients that filled multiple ACE inhibitor/ARB prescriptions during the baseline 180 days were excluded from the duplication analysis during the follow up period. It was not possible to determine if the use of multiple drugs from this class was therapeutically appropriate during the baseline period. Other contributors to the observed low frequency of duplication may be the ease of detection for healthcare providers and the use of decision support software that would flag the prescription prior to dispensing. It is also possible that patients were duplicating therapy at home from previously dispensed prescriptions, in which case we would be unable to detect such inappropriate medication usage.

The duration of prescription supply emerged as a significant confounder of the association between hospitalization and persistence. The number of patients that received a prescription supply of greater than 60 days for a study medication during the baseline period was unevenly distributed between the hospitalized and non-hospitalized groups. In the bivariate and multivariable analyses, a supply duration of greater than 60 days increased the odds of non-persistence for ACE inhibitors/ARBs and LLDs. This phenomenon may be explained by continued use of a 90 day prescription that was filled before hospital admission, or in matched patients, the sustained use of a 90 day prescription that was not due for a refill during the follow up period. In either case, patients would be at risk for being misclassified as non-persistent despite appropriate use of the study medication. Inclusion of the days' supply variable in the final model was essential in order to adjust for the effect of supply duration, which if left unadjusted would have obscured the effect of hospitalization on non-persistence. In contrast, therapeutic duplication is more likely to have been underestimated as a result of misclassification in this study. Patients choosing to continue taking a medication prescribed prior to

hospitalization, in addition to another medication within the same class prescribed upon discharge, would be inappropriately duplicating therapy. Such duplication is not detectable unless the patient refills the original prescription during the follow up period, which may not be necessary if the original supply was for greater than 60 days.

Evaluations of real-world medication usage by patients apply the terms adherence (synonym: compliance) and persistence to describe two separate constructs.[30] Other terms have been used to describe persistence (discontinuation rates, continuous adherence, persistency, time of continuous adherence), and reports have frequently stated that the endpoint under investigation was persistence when it was in fact adherence and vice versa. Medication adherence is the act of conforming to the recommendations of the provider with respect to timing, dosage, and frequency of medication taking. Medication persistence refers to the duration of time from initiation to discontinuation of therapy.[30] In our study, the outcome of persistence was dichotomized and patients were categorized as persistent or non-persistent depending on the presence or absence of a prescription claim indicating therapy continuation during a pre-specified period of time. All patients were required to have at least two claims during the baseline period prior to the index hospitalization, and a third claim during the follow up period was indicative of continued use of the medication (persistence).

The healthy adherer effect postulates that improved clinical outcomes in adherers to drug therapy compared with non-adherers is not entirely attributable to the benefits of the medication.[50] Instead, adherence to medication is a surrogate marker for overall healthy behavior, which introduces bias if left unaccounted for in an analysis of drug effect.[51] The effects of healthy adherers are not evident in our results, but a separate construct that influences medication taking behavior may be implicated.

Consistent with our hypothesis, hospitalization disrupted medication use for patients without cardiovascular disease. In contrast to our hypothesis, patients with a history of cardiovascular disease that were hospitalized were more likely to persist relative to patients with cardiovascular disease that were not hospitalized. This latter finding aligns with the tenants of the 'Necessity-Concerns Framework' conceptual model for understanding patient's perspectives on prescribed medicines.[46] A meta-analysis of 94 studies assessed the utility of this model, determining that better adherence to medications for

chronic disease was associated with stronger perceptions of the necessity of treatment [Pooled OR 1.742 (95% CI 1.569-1.934)] and fewer concerns about potential adverse effects of treatment [Pooled OR 0.504 (95% CI 0.450-0.564)].[46] Recently hospitalized patients with diabetes and comorbid cardiovascular disease may be more likely to perceive the necessity of treatment with antihypertensive medications and overlook concerns about adverse effects, contributing to the results observed in our study.

Factors associated with medication persistence are dependent upon the characteristics of the patient population, the medication class, and the data source being evaluated. A study of persistence by Gregoire et al prospectively recruited 692 patients presenting to 173 pharmacies in Ontario, Canada, with a new prescription for an antihypertensive medication from 1 of 3 classes including ACE inhibitors, ARBs, and calcium channel blockers.[52] Data were collected through a structured questionnaire during a telephone interview within five days of study entry, and again at 1 month, 3 months, and a fourth time between 18 and 32 months after enrollment. The results of a multivariate hazard model determined that the likelihood of non-persistence was greater in patients that lacked insurance coverage (odds of discontinuation in patients with any insurance coverage of 0.74; 95% CI 0.53-0.97), reported medication side effects (OR 1.91; 95% CI 1.47-2.47), or reported a belief of no drug effect (OR 1.29; 95% CI 0.97-1.71). The proportion of patients discontinuing therapy was 11.9% at 1 month, 23.8% at 3 months, and 43.3% based upon the last observation for each individual within the study period. Of these patients that were no longer on the original therapy, 32.3% had changed to another antihypertensive drug and 11% were no longer receiving drug treatment for hypertension. The survey based design was advantageous for detecting the influence of patient beliefs about drug effects on persistence, but the results of this study are also limited by the accuracy of the surveyed patient's responses and the intervals of time between survey administration.[52]

Jackevicius and colleagues assessed primary medication non-adherence to newly prescribed medications at discharge from a hospitalization due to acute myocardial infarction (AMI).[53] A retrospective cohort study was performed utilizing AMI registry data of patients from 104 hospitals in Canada. Registry data were linked to prescription claims, vital statistics, physician services, and hospital discharge databases. Patients included were at least 66 years of age upon discharge and had an

ICD-9 code for AMI. The primary outcome was death within 1 year after discharge. Primary adherence (the risk factor of interest) was categorized as all medications, some medications, or no medications filled within 120 days after the discharge date. Discharge prescriptions written for ACE inhibitors were not filled within 120 days in 3.82% of patients, while prescriptions for statins were not filled in 5.15% of patients within 120 days. Fill rates of non-cardiac medications that were assessed in this study were substantially lower than fill rates for cardiac medications (34.6% vs 82.3%; P<0.0001). A significantly increased risk of death was observed in patients that failed to fill all (OR 1.80; 95% CI 1.35-2.42) or some medications (OR 1.44; 95% CI 1.15-1.79) prescribed at discharge relative to patients that filled all prescriptions within 120 days. Receipt of pre-discharge counseling was associated with a reduced likelihood of death within 1 year (OR 0.71; 0.58-0.87). In this study prescription data was not available from private insurers and as a result only elderly patients were included. Rates of primary non-adherence following hospitalization for AMI were low, but these results are unlikely to represent younger or commercially insured populations.[53]

The findings by Gregoire et al and Jackevicius et al reinforce the proposed connection between patient perceptions of medication efficacy and the necessity for compliance and persistence with therapy.[52-53] In the survey study by Gregoire et al both patient perceived absence of drug effectiveness and the occurrence of adverse effects attributed to the drug were associated with significantly lower persistence.[52] Instead of directly reported perceptions, patients in the study by Jackevicius et al were retrospectively selected based upon recent hospitalization specifically for AMI.[53] The finding of substantially higher primary adherence rates with cardiac medications follows directly from the recognition of elevated cardiac risk that would be anticipated in patients following a hospitalization for AMI. Insurance coverage, a predictor of persistence identified by Gregoire,[52] was not a factor in our study since all patients were confirmed to be enrolled with the same commercial insurer. Additional covariates that were not associated with changes in persistence including age, gender, and comorbid disease burden were evaluated and yielded concordant results with those obtained in our present research.[52] Identification of patients that received pre-discharge counseling, a predictor of persistence in the study by Jackevicius,[53] was not possible with our commercial claims data source.

Long term use of evidence based, guideline recommended oral therapies for heart failure has been shown to reduce morbidity and mortality.[54] The Get With The Guidelines-Heart Failure program is an ongoing, prospective, observational data collection and quality improvement initiative that collects information on medical history, hospital care and clinical outcomes.[55] Krantz et al assessed the inpatient patterns of use and continuation of ACE inhibitors/ARBs, aldosterone antagonists, and beta blockers while also determining predictors of use.[56] Patients included for evaluation had reduced ejection fraction (EF<40%) heart failure and were admitted to hospitals participating in the program across the United States. In patients with no contraindication to therapy, the proportion of patients using ACE inhibitors/ARBs, beta blockers, and aldosterone antagonists at admission was 65.3%, 72.6% and 15.6%, respectively. The proportion of patients using ACE inhibitors/ARBs, beta blockers, and aldosterone antagonists at discharge was 92.9%, 90.1% and 26.2% respectively. Of the population of patients that were already receiving ACE inhibitors/ARBs at hospital admission, 2.6% did not persist with the medication at discharge. The strongest predictors of ACE/ARB usage at discharge were medication usage at admission (OR 7.4; 95% CI 4.6-11.8), the absence of concomitant renal insufficiency (OR 2.7; 95% CI 2.1-3.4), and the absence of concomitant hypertension (OR 1.34; 95% CI 1.02-1.77). These results are limited by the lack of available persistence data for the period following hospital discharge.[56]

In the study by Krantz et al patients with heart failure that were taking ACE inhibitors/ARBs upon admission into the hospital were more than 7 times as likely to be discharged on the medication compared with patients admitted that were not receiving a drug from this class.[56] Our study design included only patients that were confirmed to be using a medication from a study drug class prior to a hospital admission. We observed a proportion of patients with cardiovascular disease that did not persist with ACE inhibitor/ARB therapy of 10.26%, which was much larger than the 2.6% that did not persist in the study by Krantz et al.[56] Much of this difference can likely be explained by the definition of persistence, which was measured at discharge by Krantz and did not require confirmation of a prescription dispensing after the patient left the hospital.[56] Although persistence patterns with statins were not assessed in this population of heart failure patients, we found a comparable rate of non-persistence with statins in patients with cardiovascular disease of 10.11%.

Quality of care measures provided prior to hospitalization have been shown to impact 30 day re-hospitalization rates in a nationally representative population of commercially insured adult patients with diabetes.[57] Chen et al evaluated data from the IMS Lifelink Database to determine if receipt of 2 or more HbA1c tests, 1 or more LDL tests, at least 90 days of a statin supply dispensed, or at least 90 days of an ACE inhibitor/ARB supply dispensed in the year preceding a hospitalization reduced the odds of readmission within 30 days of discharge.[57] In a multivariate logistic regression model that adjusted for patient demographic and comorbid disease characteristics, odds of readmission were significantly decreased with the receipt of at least 1 LDL test (OR 0.92; 95% CI 0.85-0.99) or receipt of at least 90 days of a statin prescription (OR 0.91; 95% CI 0.85-0.97). Odds of readmission were marginally decreased with at least 90 days of an ACE inhibitor/ARB prescription (OR 0.94; 95% CI 0.88-1.01) or with receipt of at least 2 HbA1c tests (OR 0.94; 95% CI 0.87-1.02). The impact of the performance of quality of care measures preceding a hospitalization on readmission rates demonstrated in this study was limited by the lack of persistence data following discharge and the absence of a comparator group of non-hospitalized patients.[57]

Bell et al recently evaluated the risk of unintentional discontinuation of medications prescribed to treat chronic disease in patients undergoing 1 or more transitions of care.[6] Similar to the study by Jackevicius,[53] this study utilized linked prescription claims, vital statistics, physician services, and hospitalization databases to identify elderly patients (age > 66) admitted to all acute care hospitals in Ontario, Canada.[6] Patients were required to be continuous users for at least 1 year of at least 1 medication from 5 medication classes: statins, antiplatelets/anticoagulants, levothyroxine, respiratory inhalers, and gastric acid suppressants. Exposure was categorized into three groups: non-hospitalized patients (unexposed), hospitalized patients (1 transition of care), and hospitalized patients that spent time in the ICU (2 transitions of care). The primary outcome of interest was the absence of a prescription renewal for a drug from within the original medication class in the 90 days following the index date (the date of discharge for hospitalized and a randomly assigned date for non-hospitalized patients). Compared with non-hospitalized patients the odds of unintentional discontinuation were increased in hospitalized patients without an ICU stay [(statins: OR 1.33; 95% CI 1.29-1.37), (antiplatelets/anticoagulants: OR 1.86; 95% CI 1.77-1.97), (levothyroxine: OR 1.18; 95% CI 1.14-1.23),

(respiratory inhalers: OR 1.50; 95% CI 1.15-1.97), and (gastric acid suppressants: OR 1.50; 95% CI 1.43-1.56)] and increased further in hospitalized patients with an ICU stay [(statins: OR 1.48; 95% CI 1.39-1.57), (antiplatelets/anticoagulants: OR 2.31; 95% CI 2.07-2.57), (levothyroxine: OR 1.51; 95% CI 1.38-1.66), (respiratory inhalers: OR 1.84; 95% CI 1.10-3.08), and (gastric acid suppressants: OR 1.87; 95% CI 1.71-2.05)]. The composite secondary outcome of death, emergency department visit, or emergent hospitalization during a period of 91 days to 365 days post discharge was more likely to occur in patients that discontinued statins (OR 1.07; 95% CI 1.03-1.11) or antiplatelets/anticoagulants (OR 1.10; 95% CI 1.03-1.16) within the 90 days after discharge. These results provide valuable context for the relationship between non-persistence and adverse health outcomes in a large representative population of elderly adults following a hospitalization. Risk for adverse events following discontinuation was not equal between medication classes, with the greatest risk observed in medications used for the prevention of macrovascular events.[6]

Improving outcomes following a hospitalization, including reducing 30 day readmission rates, has become an incentivized priority with the implementation of the Affordable Care Act.[58] Underperforming hospitals with increased readmission rates for certain disease states relative to other similar institutions are subject to reduced reimbursement.[58] The results presented by Chen suggest that adherence to recommended processes of care for commercially insured patients with diabetes will positively influence 30 day readmission rates.[57] Bell and colleagues demonstrated that appropriate use of chronic medications in elderly patients is disrupted incrementally by 1 or more transitions of care. Furthermore, non-persistence following a hospitalization with medications for the prevention of adverse macrovascular outcomes (statins, antiplatelets/anticoagulants) placed elderly patients at an increased likelihood for 1 year mortality and rehospitalization.[6] Our study evaluated a commercially insured population, similar to Chen,[57] but persistence after a hospitalization was measured with medication classes used for the prevention of micro and macrovascular outcomes, similar to Bell.[6] Considering these relevant findings, our results indicate that patients with diabetes and comorbid cardiovascular disease that were not hospitalized, as well as patients hospitalized without cardiovascular disease, may also be at an increased risk of adverse health outcomes due to lower rates of persistence. Further studies

designed to follow persistence patterns and evaluate health outcomes are necessary in patients with diabetes.

Based upon our multivariable model, certain populations of LLD users are possibly at greater risk of unintentional discontinuation of LLD therapy. A non-significant trend was observed for decreasing comorbid disease burden associated with increasing odds of non-persistence (Table 3a). Similarly, patients without documented use of a medication for diabetes treatment during the baseline period were the least likely to persist with LLD therapy. An opposite tendency was demonstrated with regards to regimen complexity. In agreement with our hypothesis, patients using the least number of medications during the baseline period had the greatest relative likelihood of persisting. These conflicting phenomena are presumed to be the consequence of multiple contributing factors and random variation. Healthier patients with diabetes that were not using hypoglycemic medication and had a minimal burden of comorbid disease may not have perceived LLD treatment as necessary and were consequently at an increased risk for non-persistence. In addition to polypharmacy, the regimen complexity variable may have captured a separate indicator of disease burden that was not fully reflected in the comorbidity score grouping and was associated with an increased risk for non-persistence. Ultimately the main result of the LLD multivariable analysis was that after adjusting for all possible confounders, there was no difference in odds of persistence between non-hospitalized and hospitalized patients with diabetes (0.961 [0.469 - 1.972]).

Studies evaluating relative rates of mortality and other adverse health outcomes between adherent/persistent patients with non-adherent/non-persistent patients have demonstrated that appropriate usage of statins and ACE inhibitors/ARBs is associated with better clinical outcomes.[6-7, 33-38] This result should be expected when these drugs are used for evidence based indications in patient populations for which expert professional organizations have published guidelines recommending their use.[40-41, 54] A more difficult question involves the determination of what level of patient adherence is necessary to achieve the beneficial effects of the medication before a difference in clinical outcomes is manifested. This uncertainty applies indirectly to persistence. When the definition of persistence is established for a study protocol, it is necessary to identify what period of time must elapse between the dispensing of two prescriptions that is indicative of non-persistence. A longer permissible gap will

directly translate into a lower acceptable level of adherence that is necessary to remain persistent. In our present study, a period of 60 days without a prescription claim for the medication was used. Assuming a 30 day prescription supply (87.31% of the LLD cohort, 85.04% of the ACE inhibitor/ARB cohort), if the patient filled a prescription immediately prior to the beginning of the 60 day follow-up period then an adherence level of 50% would be sufficient to last the 60 days without another prescription fill. An adherence level greater than 50% would result in a refill during this period confirming persistence, but the proportion of therapeutic effect achieved by a persistent patient with reduced adherence remains uncertain.

Rasmussen et al addressed the problem of relative risk for incremental levels of adherence in a population of elderly adults (age $\geq$66) in Ontario, Canada, following a hospitalization for AMI.[33] For inclusion into the study, all patients were required to fill a prescription for either a statin, beta-blocker, or calcium channel blocker in the 3 months after hospital discharge. In the year following dispensing of the first study medication, the proportion of days covered (PDC) was determined and levels of adherence were subdivided into 3 categories (high adherence: PDC $\geq$ 80%; intermediate adherence: PDC $\geq$ 40%-79%; and low adherence: PDC $\geq$ 40%). The primary outcome of long term mortality was assessed over a median period of 2.4 years. Non-persistence was determined over the full period of follow up and defined as the absence of an expected prescription based upon previous quantities supplied, evaluated over 6 month periods from each previous prescription dispensing. Non-persistence at the end of follow up was 13.2%, 19.6% and 33.5% for statins, beta blockers, and calcium channel blockers, respectively. A dose-response type relationship was observed with the risk of mortality (HR; 95% CI) increasing with decreasing levels of adherence with statins [(intermediate adherence: 1.12; 1.01-1.25), (low adherence 1.25; 1.09-1.42)] and beta blockers [(intermediate adherence: 1.01; 0.93-1.09), (low adherence 1.13; 1.03-1.25)]. This relationship was stronger with statins than with beta blockers, and was not detected with calcium channel blockers. The absence of an adherence-mortality relationship for calcium channel blockers, a medication class which does not have any proven post-AMI survival advantages, supports the attribution of a survival benefit for the other medication classes to drug effect rather than the healthy adherer effect. [33]

Recognition of the detrimental outcomes occurring secondary to inappropriate management of the medication regimen during care transitions has lead to the development and evaluation of numerous institution specific interventions.[15-16] Due to the fragmented nature of the United States health system and the logistical difficulties in organizing large multi-site trials, stakeholders have typically approached the issue individually as it directly relates to a specific practice population, professional discipline, or institution. Individualized programs targeting care transitions have involved a multitude of different healthcare providers including nurses,[17-19] physicians,[20] pharmacists,[17-19,21-23] pharmacy technicians,[24,28] and nurse practitioners.[25-26] Examples of interventions include medication reconciliation at admission and or discharge, post discharge phone calls or home visits, motivational coaching and education, or a combination of multiple interventions.[17-28] These interventions have yielded varying degrees of success on clinical and surrogate outcomes, with limited generalization to larger populations.

Care transition interventions are often compared with the standard of care provided prior to implementation of the intervention at the institution.[20, 23-25] A systematic review of the literature by Kripalani et al sought to characterize the types and prevalence of deficits in communication between hospital based and community based physicians at hospital discharge.[20] A total of 55 observational studies that had been published from 1970 through 2005 were included. In these studies, 3% of primary care physicians reported being involved in discussions about discharge and 17-20% reported always being notified of discharges. Within 1 week of discharge, a median of 53% (30-94%) of discharge letters and 14.5% (9-20%) of physician dictated discharge summaries had reached the primary care physician. In addition, 11% of discharge letters and 25% of discharge summaries never reached the primary care physician. Interventional studies included in the review involved either provision of computer generated and manually created discharge summaries, changes in the mode of information delivery, or reformatting of the discharge documents. No standardized measures were used across studies, and results indicated a mix of significant and non-significant improvements in timeliness of discharge communication. This systematic review of the literature emphasizes the historical inefficiencies of hospital physician to outpatient physician communication and the limited application of institution specific interventions for broader health system improvement.[20]

Pharmacist intervention during care transitions has demonstrated varying levels of success. [17-19,21-23] A randomized controlled trial that assessed pharmacist counseling at discharge was carried out at a single academic hospital in Boston, Massachusetts.[18] Routine care involved the review of medication orders by the ward based pharmacist and discharge counseling provided by a nurse, which sometimes consisted of informal medication reconciliation. The multifaceted pharmacist intervention consisted of evaluation for previous drug related problems (side effects, non-adherence), reconciliation of discharge medications with admission medications, and the review of discharge medications with the patient. A follow-up phone call 3 to 5 days after discharge was also performed by the pharmacist. During the phone call, medication use by the patient was reconciled with discharge medication instructions and adherence to post hospital care was assessed and communicated to the outpatient primary care physician. A significant reduction in preventable ADE's (1% intervention vs 11% usual care; P=0.01) was observed at 30 days post discharge. The total number of ADEs and resource utilization was similar between groups, but the number of preventable medication related emergency department visits and readmissions was reduced in the intervention group (1% vs 8%; P=0.03). Pharmacists are capable of performing medication reconciliation, and were shown to beneficially impact post discharge medication use. The small number of patients participating in the trial and the short period of follow up may have limited the ability to demonstrate an overall reduction in ADEs and resource utilization.[18]

Another randomized controlled study conducted at an academic hospital in Boston, Massachusetts, achieved improvements in post discharge hospital utilization with coordinated discharge intervention by a nurse and pharmacist.[19] A nurse discharge advocate arranged follow up appointments, reconciled medications with outpatient records, and conducted inpatient education. The pharmacist performed follow-up phone calls in the week post discharge to perform a medication review and subsequent corrective action as needed. Compared to usual care, the 30 day combined re-hospitalization and emergency department visit rate was reduced (incident rate ratio: 0.695; 95% CI 0.515-0.937). The proportion of patients following up with their primary care provider after discharge was significantly greater in the intervention group (62% vs 44%; P=0.007). The nurse discharge advocate spent an average of 87.5 minutes, and the pharmacist an average of 26 minutes, per patient providing intervention related services. A cost analysis considering the cost of follow up appointments and

hospitalization determined that an estimated $412 per person was averted in the intervention group compared with usual care. This estimation was limited since it did not account for the cost of the intervention, although it was determined that the intervention could be partially implemented using the present hospital employee structure. The authors concluded that in a traditional fee for service model, the additional services provided by the intervention would not be incentivized through reimbursement and would be less likely to be implemented than in a capitated or pay-for-performance model.[19]

Other studies have been unable to demonstrate a clear benefit of pharmacist intervention during care transitions.[21, 23] One randomized controlled study investigated the effect of an integrated pharmacy discharge plan involving hospital and community pharmacists from 4 hospitals and 29 community pharmacies.[23] The intervention involved hospital pharmacist development of medication and supportive discharge plans for provision to all necessary healthcare providers, as well as a home follow up visit by a community pharmacist after discharge. The comparison group received usual care, consisting of a discharge letter to the PCP and no pharmacist pre-discharge medication review. No significant difference was found with regards to the primary outcome of 6 month readmission between the control (28.4%) and intervention groups (27.9%). Secondary endpoints measured included adherence, comprehension, mortality, and healthcare usage. Similar results on the secondary outcomes were reported for both groups.[23]

A care transition intervention implemented by Coleman et al utilized strategic patient and caregiver education.[25] The objective of the patient focused intervention was to prepare for future self-management of the medication regimen during care transitions and provider interactions. Community dwelling elderly adults (age $\geq$ 65) were recruited upon admission to the study hospital located in Colorado. A total of 158 patients were included in the intervention and matched to administrative controls derived from a managed care delivery system with an existing contract with the study hospital. Patients and their caregivers that received the intervention were provided with tools and support in order to actively participate in the transition from hospital to home. A geriatric nurse practitioner served as a transition coach, contacting the patient via telephone and visiting for home visits. The transition coach performed medication reconciliation during the home visit, and assisted in preparing the patient for handling future interactions with care providers. The median duration of the intervention for an

individual patient was 24 days. The primary outcome was the odds of rehospitalization, which was significantly reduced in the intervention group at 30 days (OR 0.52; 95% CI 0.28-0.96), 90 days (OR 0.43; 95% CI 0.25-0.72) and 180 days (OR 0.76; 95% CI 0.36-0.92) after hospital discharge. The results of this study are limited by the quasi-experimental design but suggest that an initial investment in patient education by a specialized transition coach is successful in reducing future resource utilization. A cost effectiveness evaluation of a similar intervention, evaluated prospectively in a larger population, would help inform further development of coaching based care transition interventions.[25]

Inconsistent results have been reported from a multitude of institution or region specific studies that have evaluated interventions targeting transitions of care.[15-26] The importance of standardization is implicit in the High 5s project presently being implemented internationally by participant countries within the World Health Organization.[27-29] The demonstrable implementation and evaluation of standardized operating procedures (SOPs) across different cultural, geographic, and medical care settings involved in this project has been proposed as preferable to the traditional medical approach of individualized best practice.[29] Early results of the SOP for medication reconciliation have been positive, demonstrating reduced incidence of medication errors upon admission for elderly patients.[27-28] Use of a standardized procedure has contributed to distinct obstacles during implementation of the SOP.[29] Hospitals utilizing pharmacy technicians to obtain a complete medication history have outperformed hospitals with physician or nursing based models.[28] This differential outcome from the same underlying process draws attention to potential difficulties encountered with a standardized approach. Expertise is not entirely coincident between practice disciplines and allocation of responsibility to specific healthcare practitioners will be inconsistent between institutions. The success of the SOP for medication reconciliation, if sufficiently validated, will still require cross-disciplinary collaboration and tailoring of the SOP to best function within individual practice sites.

CHAPTER 5

LIMITATIONS AND CONCLUSION

The present study utilized a retrospective matched cohort design to ensure that hospitalized and non-hospitalized patients were similar with regards to age, gender, comorbidity burden and enrollment period. The purpose of matching in this study was to ensure that the group of non-hospitalized patients was similar to the group of hospitalized patients. Despite the matching procedure, a significantly higher percentage of hospitalized patients had diagnoses indicating respiratory and cardiovascular disease, and mental health disorders. While our multivariate analyses attempted to control for these differences, it is possible that the effect of hospitalization on medication persistence was biased by the greater overall disease burden among the hospitalized group. Due to the retrospective, non-randomized study design and the use of claims data it was not possible to adjust for all possible confounders. As a result, the potential for uncontrolled residual confounding existed due to additional variables that may have included but were not limited to socioeconomic status, healthcare service utilization, delivery of medication counseling, education level achieved, and patient perceptions regarding benefits and detriments of pharmacy care services. An additional limitation was the breaking of matches after the matching procedure had been completed that caused minor inequalities between the size of hospitalized and non-hospitalized patient populations in both study drug cohorts. This resulted from exclusion of patients that did not have a prescription claim during the follow up period. This procedure was necessary to prevent misclassification of patients no longer filling prescriptions with the insurer as non-persistent, but it may have further contributed to the unequal distribution of confounders between groups.

The primary outcome of interest, persistence, is a surrogate marker for adverse health outcomes that are expected to follow the inappropriate discontinuation of evidence based therapies for chronic disease. A comparison of readmission and/or mortality rates between persistent and non-persistent patients would be useful to fully characterize the adverse effects of medication disruption by inpatient hospitalization. Moreover, the potential for misclassification surrounding the primary outcome

must be considered. Although the medication classes selected for this study are recommended for use in broad populations of patients with diabetes,[39] it is possible that the medications were intentionally stopped by prescribers for legitimate reasons. Such causes may have included intolerable adverse effects, newly developed contraindications to therapy, or lifestyle control of the medical condition that precluded the necessity for continued drug treatment. Detection of prescription fills for persistence confirmation was also limited to claims submitted to the commercial insurer. Prescriptions that were bought without insurance or with alternative insurance coverage would not be detected and patients would be at risk for misclassification. We sought to mitigate such bias through the exclusion of patients that did not have a prescription claim for any medication during the follow up period. Our exclusion of such patients contributed to an underestimation of persistence if it is presumed that these patients filled their prescription without reimbursement from Blue Cross Blue Shield of Rhode Island. With claims data, adherence to prescription medications is determined using the surrogate marker of a prescription dispensing. It is possible that patients picked up medication but then did not proceed to take it, resulting in misclassification of baseline adherence or follow up persistence.

Our study is believed to be the first to evaluate persistence patterns following hospitalization in a commercially insured population with diabetes that was adherent to evidence based therapy prior to hospitalization. The use of a matched comparator group of patients with diabetes that were not hospitalized sought to preclude the introduction of bias and improved the interpretability of our results. The capacity for generalization of our results is limited to a commercially insured population with diabetes using ACE inhibitors/ARBS or LLDs. Further research evaluating persistence and successive clinical outcomes in this population is required to better characterize the impact of regimen disruption secondary to hospitalization. Confirmation of our results is also warranted in nationally representative populations of elderly and commercially insured patients with diabetes. Future studies using outpatient claims data would be improved through an integrated analysis with inpatient and outpatient medical records, which would increase the specificity for identifying true non-persistence. Intentional medication discontinuation would be detectable in the medical chart, comorbid disease burden would be verifiable, and information on additional potential confounders would be available for assessment. Ideally, medical records and claims data will be used together to evaluate the effect of a care transition

intervention, such as medication reconciliation, in a randomized prospective study conducted across multiple institutions. Such a large scale and rigorous study methodology is necessary to generate widely applicable evidence of improved clinical outcomes and to justify funding and implementation of specific care transition interventions.

In conclusion, hospitalization was found to be a significant risk factor for ACE inhibitor/ARB discontinuation in commercially insured patients with diabetes without comorbid cardiovascular disease. Hospitalized patients with cardiovascular disease were more likely to persist with ACE inhibitor/ARB therapy than non-hospitalized patients with cardiovascular disease. Hospitalization was not found to disrupt continuation of LLD treatment after discharge, as persistence rates were similar to non-hospitalized patients. A prescription supply of greater than the number of days in the follow up period was identified as a strong confounder of persistence with both drug classes. Prescription supply duration should be considered in future studies measuring persistence. Further evaluation of the disruptive impact of hospitalization on appropriate medication use in patients with diabetes should focus on quantifying increased risk of adverse health outcomes with non-persistence and the effectiveness of care transition interventions on preventing unintentional medication discontinuation.

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APPENDIX A

ICD-9 CODES TO IDENTIFY DIABETES

25000 25001 25002 25003 25010 25011 25012 25013 25020 25021 25022 25023 25030 25031
25032 25033 25040 25041 25042 25043 25050 25051 25052 25053 25060 25061 25062 25063
25070 25071 25072 25073 25080 25081 25082 25083 25090 25091 25092 25093 3572 36201
36202 36203 36204 36205 36206 36207 36641 64801 64802 64803 64804

APPENDIX B

HEDIS 2009 CPT CODES TO IDENTIFY VISIT TYPE

Nonacute Inpatient CPT Codes

99301 99302 99303 99304 99305 99306 99307 99308 99309 99310 99311 99312 99313 99315 99316 99318 99321 99322 99323 99324 99325 99326 99327 99328 99331 99332 99333 99334 99335 99336 99337

Acute Inpatient CPT Codes

99221 99222 99223 99231 99232 99233 99238 99239 99251 99252 99253 99254 99255 99261 99262 99263 99291

APPENDIX C

MEDICATIONS WITHIN EACH STUDY MEDICATION CLASS

Ace Inhibitors and Angiotensin Receptor Blockers (ARB)	**Lipid Lowering Drugs (LLD)**
Aliskiren	Atorvastatin Calcium
Aliskiren/Hydrochlorothiazide	Amlodipine Besylate/Atorvastatin Calcium
Benazepril Hydrochloride	Cholestyramine
Benazepril Hydrochloride/Hydrochlorothiazide	Colesevelam Hydrochloride
Candesartan Cilexetil	Colestipol Hydrochloride
Candesartan Cilexetil/Hydrochlorothiazide Captopril	Colestipol Hydrochloride, Micronized
Captopril/Hydrochlorothiazide	Ezetimibe
Enalapril Maleate	Ezetimibe/Simvastatin
Enalapril Maleate/Hydrochlorothiazide	Fenofibrate
Eprosartan Mesylate	Fenofibrate, Micronized
Fosinopril Sodium	Fenofibric Acid
Fosinopril Sodium/Hydrochlorothiazide	Fluvastatin Sodium
Hydrochlorothiazide/Irbesartan	Gemfibrozil
Hydrochlorothiazide/Lisinopril	Lovastatin
Hydrochlorothiazide/Moexipril Hydrochloride	Lovastatin/Niacin
Hydrochlorothiazide/Losartan Potassium	Niacin
Hydrochlorothiazide/Olmesartan Medoxomil	Niacin/Simvastatin
Hydrochlorothiazide/Quinapril Hydrochloride	Omega-3-Acid Ethyl Esters
Hydrochlorothiazide/Telmisartan	Pravastatin Sodium
Hydrochlorothiazide/Valsartan	Rosuvastatin Calcium
Irbesartan	Simvastatin
Lisinopril	
Losartan Potassium	
Losartan Potassium	
Moexipril Hydrochloride	
Olmesartan Medoxomil	
Perindopril Erbumine	
Quinapril Hydrochloride	
Ramipril	
Telmisartan	
Trandolapril	
Trandolapril/Verapamil	
Valsartan	

APPENDIX D

COMORBIDITY SCORE DISTRIBUTION BY MEDICATION CLASS
(Patients that were eligible for matching and were matched)

Comorbidity Score	**ACE/ARB (N=207 each group)[a] % (N)**	**LLD (N=206 each group)[b] % (N)**
0	55.56 (115)	53.40 (110)
1	15.94 (33)	11.65 (24)
2	15.46 (32)	16.99 (35)
3	6.28 (13)	8.74 (18)
4	2.90 (6)	3.40 (7)
5	0.48 (1)	0.49 (1)
6	0.97 (2)	1.94 (4)
7	0.97 (2)	1.46 (3)
8	0.97 (2)	0.49 (1)
9	0 (0)	0.97 (2)
10	0.48 (1)	0.49 (1)

[a] 207 hospitalized and non-hospitalized patients each (total 414)
[b] 206 hospitalized and non-hospitalized patients each (total 412)

APPENDIX E

CONFOUNDER ASSESSMENT

ACE Inhibitor/ARB Cohort

Multivariable Logistic Regression Model	Parameter Estimate (β)	P-value
Full Model[a]	-0.931	0.028
Full Model - Age	-0.911	0.030
Full Model - Gender	0.931	0.028
Full Model - Comorbidity Score Group	-0.929	0.028
Full Model - Respiratory Disease	-0.915	0.031
Full Model - Mental Health Disease	-0.936	0.027
Full Model - Days' Supply	-0.662	0.092
Full Model - Regimen Complexity	-0.811	0.047
Full Model - Diabetes Severity	-1.011	0.016

[a] The full model was the standard for comparison and consisted of all potential confounders and the two-way interaction between hospitalization and cardiovascular disease

APPENDIX E

CONFOUNDER ASSESSMENT

Lipid Lowering Drugs

Multivariable Logistic Regression Model	Parameter Estimate (β)	P-value
Full Model[a]	-0.040	0.914
Full Model - Age	-0.037	0.920
Full Model - Gender	-0.040	0.914
Full Model - Comorbidity Score Group	-0.122	0.735
Full Model - Cardiovascular Disease	-0.040	0.913
Full Model - Respiratory Disease	-0.074	0.839
Full Model - Mental Health Disease	-0.036	0.922
Full Model - Days' Supply	0.197	0.572
Full Model - Regimen Complexity	-0.181	0.607
Full Model - Diabetes Severity	-0.107	0.765

[a] The full model was the standard for comparison and consisted of all potential confounders

APPENDIX F

Calibration Assessment of the Final Multivariable Logistic Regression Model

Model	Hosmer and Lemeshow Goodness of Fit	C Statistic
Final ACE inhibitor/ARB Model[a]	0.23	0.77
Final LLD Model[b]	0.87	0.73

[a] The final model consisted of all potential confounders and the two-way interaction between hospitalization and cardiovascular disease
[b] The final model consisted of all potential confounders

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