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Impact Of Time-Varying And Time-Invariant Measures Of Adherence To Secondary Prevention Therapies Post-Acute Myocardial Infarction: An Application Of Marginal Structural Models (Msms)

Tasneem Taher Lokhandwala
University of Mississippi

IMPACT OF TIME-VARYING AND TIME-INVARIANT MEASURES OF ADHERENCE TO SECONDARY PREVENTION THERAPIES POST-ACUTE MYOCARDIAL INFARCTION: AN APPLICATION OF MARGINAL STRUCTURAL MODELS (MSMS)

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TASNEEM LOKHANDWALA

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ABSTRACT

The purpose of the study was to explore the relationship between patient adherence to secondary prevention therapies post an initial episode of acute myocardial infarction (AMI) and subsequent risk of cardiovascular events by using time-invariant and time-varying measures of adherence. The effectiveness of both measures in predicting a (i) recurrent AMI, and (ii) mortality using various mathematical models and statistical techniques was compared. Time dependent confounding was accounted for by using marginal structural models (MSMs).

A longitudinal cohort observational study design was employed using the retrospective Medicare 5% random national sample claims data from January 1st, 2006 to December 31st, 2008. The time-invariant measure of adherence was measured over a fixed one year period. Time-varying adherence was measured quarterly along with other time-varying confounders over a maximum follow-up of 11 quarters. Estimates of the effect of adherence from Cox regression models and MSMs were compared, along with model-fit-statistics.

Of the total 1,427 patients included in the study, cohort A (statin therapy) comprised of 1,091 patients, and cohorts B (β-blocker therapy) and C (angiotensin converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) therapy) included 1,021 and 1,025 patients, respectively. When accounting only for baseline covariates in a discrete-event time model the hazard for a recurrent AMI among statin adherent patients in cohort A was 63% of the hazard among non-adherent patients (Hazard Ratio (HR) = 0.63; 95% CI [0.40, 0.99]; $p = 0.0471$). When accounting for baseline covariates and time-varying covariates in a discrete-event time

model the hazard for a recurrent AMI among statin adherent patients in cohort A was 61% of the hazard among non-adherent patients (HR = 0.61, 95% CI [0.38, 0.97]; $p = 0.0366$). The results for the effect of adherence to β-blockers and ACEI/ARBs on subsequent cardiovascular events were not statistically significant. The stabilized weights used in estimation of the MSMs did not have optimum variability and the results from the MSMs were not statistically significant.

Further studies are required to understand if MSMs should be the preferred methodology when exploring the relationship between long-term medication adherence and health outcomes.

LIST OF ABBREVIATIONS

ACC	American College of Cardiology
ACEI	Angiotensin converting enzyme inhibitor
ACS	Acute coronary syndrome
AIC	Akaike information criterion
ARB	Angiotensin receptor blocker
AMI	Acute myocardial infarction
BIC	Bayesian information criterion
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCI	Charlson's comorbidity index
CDC	Centers of Disease Control and Prevention
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DUA	Data Use Agreement
ER	Emergency room
ESRD	End stage renal disease
HMO	Health maintenance organization

HR	Hazards ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IPTW	Inverse probability of treatment weights
IRB	Institutional Review Board
MPR	Medication possession ratio
MSM	Marginal structural model
NDC	National Drug Code
OR	Odds ratio
PCI	Percutaneous coronary intervention
PDC	Proportion of days covered
ReComp	Refill Compliance
RIF	Research identifiable files
SAS	Statistical Analysis Software

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CHAPTER 1

INTRODUCTION

Adherence to Secondary Prevention Therapies Post-Acute Myocardial Infarction

Cardiovascular disease (CVD) continues to be responsible for the most number of deaths in the United States (U.S.) every single year since 1900, with the exception of 1918 (Roger et al., 2012). The economic burden of the disease too, is crippling. As per the Heart Disease and Stroke Statistics 2012 update, acute myocardial infarction (AMI) is one of the major contributors of the morbidity, mortality, and economic burden attributable to CVD (Roger et al., 2012). Clinical guidelines recommend indefinite treatment with statin, β-blocker, aspirin, and angiotensin converting enzyme inhibitor (ACEI)/ angiotensin receptor blocker (ARB) therapy post-AMI to prevent recurrent AMI and mortality (Smith et al., 2011). Even though multiple clinical trials suggest that secondary prevention therapies post-AMI are beneficial (see Hennekens, Albert, Godfried, Gaziano, & Buring, 1996 for a review), meta-analysis of observational studies suggest that long-term adherence to these drug classes is not optimal (Naderi, Bestwick, & Wald, 2012). The recent meta-analysis reported a summary estimate of 57% for adherence to primary and secondary prevention therapies among patients with CVD. Patients who had at least 75% of days covered for a specific drug over a specified time period

were classified as adherent. Among AMI patients only one third were found to adhere to secondary prevention therapies.

Given that long-term adherence is suboptimal, it is essential to understand its effects on subsequent outcomes. However, it is not possible to explore this relationship using clinical trials, as subjects cannot be randomly assigned to adhere to drug therapies. Observational studies are the most feasible, economical, and pragmatic tool to measure long-term adherence among real-world patients and its association with outcomes thereof. There are several observational studies that aim to explore the relationship between use of secondary prevention therapies at discharge post-AMI and outcomes, and report beneficial effects of therapy (Ho et al., 2006; Jackevius, Li, & Tu, 2008; Lee, Cooke, & Robertson, 2008). These studies, however, have not measured long-term adherence and its effect on subsequent outcomes. They have defined use of secondary prevention therapy as possession of medication at discharge, or 30 days after discharge. The association between use of secondary prevention therapy as described above and outcomes measured over a year after discharge cannot be termed causal. There are a number of other factors that could lead to the outcomes over the year. Studies that have measured long-term adherence generally compute it as a constant medication possession ratio (MPR)/proportion of days covered (PDC) over a year post-discharge. The association between this long-term adherence and outcomes over the entire period is then reported, which sometimes extends to five years or more, while adjusting for baseline covariates (Newby et al., 2006; Rasmussen, Chong, & Alter, 2007; Amin, Mukhopadhyay, Nathan, Napan, & Kelly, 2009). In other cases the adherence is measured as a constant over a certain period of time, and its correlation with outcomes measured during the same time period is reported (Wei et al., 2002). Studies have also reported the association between persistence and outcomes (Gislason et al., 2007), where

persistence is defined as time to break in therapy for a pre-defined number of days which varies across study designs. However, it has been shown that some patients resume therapy after a break.

One drawback of trying to study the effect of long-term adherence on subsequent outcomes using the above methods is that medication adherence is not static. It is a dynamic process that may change over time due to the effect of intermediate events. To my knowledge, there are not many studies that have modeled adherence to secondary prevention therapies post-AMI as a time-varying predictor to study its effects on outcomes. Studies that have attempted to do so have used the Cox proportional hazards model with adherence as a time-varying predictor (Ho et al., 2008; Levy, Tamblyn, Abrahamowiez, Mc Leod, & Fitchett, 2004), which seems like a simple solution. However, it has been suggested that using this approach will not provide estimates with a causal interpretation in the presence of time-dependent confounding (Robins, Hernan, & Brumback, 2000; Hernan, Hernandez-Diaz, & Robins, 2004; Hernan, Robins, & Garcia Rodrigues, 2005).

Time-Dependent Confounding

In most health intervention research, the exposure varies with time and so do the covariates. In most cases, the time-varying confounders are outcomes of previous exposure. They are also predictors of subsequent exposure and outcomes. Therefore, these variables are interrelated and form a sort of feedback loop or cycle. However, most researchers ignore this and study these as independent variables while trying to estimate the causal effect of one on another. This is applicable in the case of studying the effect of medication adherence on subsequent outcomes (Morris & Schulz, 1992).

To understand this phenomenon and how it might lead to biased results in our case, consider the longitudinal effect of disease severity while studying the effect of adherence on subsequent outcomes (Figure I). Disease severity is a dynamic measure; however most researchers adjust for the number of hospital/emergency room (ER) visits, concomitant medications and so on, as a constant variable measured over the entire study period. Based on prior literature, medication adherence (at any time *t*), is a behavior that reduces the risk of subsequent mortality (at *t+1*). Disease severity is associated with adherence at *t* and also the subsequent risk of mortality, making disease severity at *t-1* a confounder. Additionally, medication adherence at *t* has an effect on disease severity at *t+1*, thus disease severity at each t_n is related to prior exposure. Therefore, here a crude estimate between adherence at *t* and mortality at *t+1* will be biased as subjects with low adherence measures at *t* will tend to be those that differ in disease severity at *t-1* and have a higher risk of mortality at *t+1*. The estimate obtained after adjusting for disease severity at *t-1* will be biased as it does not account for the fact that after the start of the study the level of adherence may change according to changes in disease severity and vice versa. Even controlling for repeated measures of disease severity may not be the solution to the problem, due to the presence of the feedback loop where disease severity is on the pathway between adherence and mortality (Cole, & Hernan, 2002; Greenland, 2003; Hernan et al., 2004).

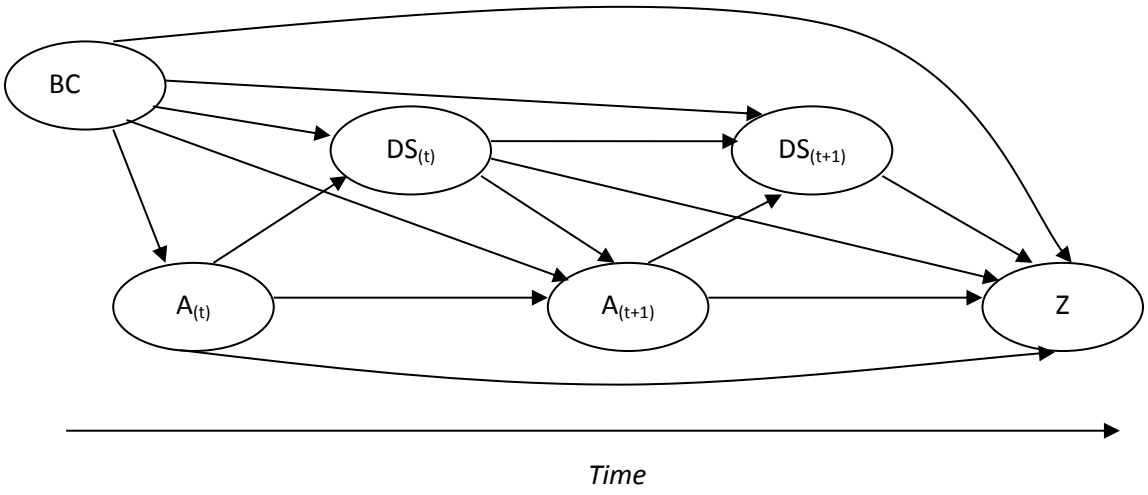

Figure I Longitudinal effect of time-dependent confounders. *$DS_{(t)}$* and *$DS_{(t+1)}$* represent disease severity at time *t* and *t+1,* respectively. Similarly, *A(t)* and *A(t+1)* represent adherence at times *t* and *t+1,* respectively. *Z* denotes the outcomes and *BC* stands for the baseline covariates which includes *DS(t-1).*

Since traditional methods that have been used predominantly in the literature do not account for bias due to time-dependent confounding, a relatively new estimation method – marginal structural models (MSMs) was developed and proposed by Robins and colleagues (Robins, 1999; Robins et al. 2000). Inverse probability of treatment weights (IPTWs) are used in the estimation of MSMs, where the inverse probability of receiving the actual treatment given prior covariate history are used as weights that essentially produce a pseudo-population. This accounts for the time-dependent confounding, as the adherence at a particular time is no longer predicted by the covariates, enabling one to generate an unbiased estimate of the effect of long-term adherence on outcomes. In addition to the patient-specific weights, time-specific weights adjusting for study discontinuation are used in the final model. The use of these models in the literature has been scarce so far. Studies that have employed this technique, however, have reported differences in estimates with MSMs and those obtained by traditional methods (Hernan, Brumback, & Robins, 2000; Bodnar, Davidian, Siega-Riz, & Tsiatis, 2004; Teng et al., 2005;

Cole, Hernan, Margolick, Cohen, & Robins, 2005). They recommend the use of MSMs in the presence of time-dependent confounding.

Needs Assessment

Considering the above, the estimates of the causal effects of adherence on subsequent outcomes may be biased due to time-dependent confounding. There has been only one study that uses MSMs to estimate the effect of β-blocker use on subsequent mortality (Delaney, Daskalopoulou, & Suissa, 2009). β-blocker use is not a time-varying predictor in their study and the clinical measure of blood pressure is the only time-varying confounder that was modeled. The objective of this study, however, is to measure the effect of long-term adherence to secondary prevention therapies post-AMI on subsequent outcomes, and not the effect of the use of the drugs at discharge on outcomes.

With the economic burden of the disease being high, and the suboptimal levels of adherence to secondary prevention therapies, it is imperative to try and obtain an un-biased estimate of the effects of long-term adherence to secondary prevention therapies post-AMI on subsequent outcomes. Additionally, it is important to understand the extent of the protective effect of adherence while designing interventions and disease management programs for patients with AMI.

From a methodology perspective, too, this study is significant. As mentioned before, observational studies are the most suitable for studying the effect of long-term adherence on subsequent outcomes. A meta-analysis conducted by DiMatteo, Giordani, Lepper, and Croghan (2002) identified 44 articles that explored this relationship. The authors stated that the studies were all co-relational in nature, and hence there is a need to perfect the methods used to explore

this relationship. Gu (2011) used Cox proportional hazard models and pooled logistic regressions to investigate the relationship between adherence to antihypertensives and cardiovascular outcomes with adherence measured as time-constant and time-varying. Various models were compared and it was concluded that both measures were similar in predicting adherence. However, the study did not account for time-varying confounding. Similarly, Yu, Yu, and Nichol (2010) have compared various models using adherence to hypoglycemics as time-constant and time-varying predictors to predict outcomes among type 2 diabetes patients. They found that the various models yielded very different estimates among which only estimates from MSMs suggested a reduced risk of complications among patients with higher adherence measures. From above, it is evident that there is a need for additional studies among patients with varied chronic conditions to determine the best methodology required to explore the relationship between long-term adherence and subsequent outcomes using observational studies.

Study Aims

The broad purpose of the study was to explore the relationship between patient adherence to secondary prevention therapies post an initial episode of AMI and subsequent risk of cardiovascular events by using two approaches to measure adherence. A time-invariant and a time-varying measure of adherence were computed and the effectiveness of both in predicting subsequent outcomes using various mathematical models and statistical techniques was compared. The specific aims of the study were:

1. To explore the predictors of patient adherence to secondary prevention therapies post-AMI.

2. To explore the relationship between adherence to secondary prevention therapies post-AMI measured as a time-invariant variable and the risk of subsequent outcomes.
3. To explore the relationship between adherence to secondary prevention therapies post-AMI measured as a time-varying variable and the risk of subsequent outcomes.
4. To compare the effectiveness of measuring adherence as a time-invariant and time-varying predictor of subsequent outcomes.

CHAPTER 2

LITERATURE REVIEW

Health and Economic Burden of Cardiovascular Disease and Acute Myocardial Infarction

An estimated >1 in 3 Americans have one or more types of cardiovascular disease (CVD), which accounted for 32.8% of all deaths in the U.S. in 2008 according to the 2012 update of the Heart Disease and Stroke Statistics (Roger et al., 2012) released by the American Heart Association (AHA). In the past century, it has been the leading cause of death in the country consistently, based on the estimates from the National Center for Health Statistics (NCHS) and Centers for Disease Control and Prevention (CDC). The estimated direct and indirect cost for CVD in 2008 is $297.7 billion and is projected to increase to thrice that figure by 2030 (Heidenreich et al., 2011). Thus, CVD and especially, AMI remain a burden to the country in terms of costs accumulated and mortality rates. The overall prevalence for AMI is 3.1% in U.S. adults, over 20 years of age, based on the data from NHANES 2005-2008, with the prevalence in men (4.35%) being slightly higher than that in women (2.2%) (Roger et al., 2012). As per the 2012 update of the Heart Disease and Stroke Statistics, the estimated annual incidence of AMI is 610,000 new attacks and 325,000 recurrent attacks with the average reported age at first AMI being 64.5 years for men and 70.3 years for women. Approximately every 34 seconds an American will experience an AMI and ≈15% of the patients that experience an AMI will die of it (Roger et al.,

2012). Additional computations suggest that an approximate of 16.6 average number of years of life are lost due to AMI. Age-adjusted hospitalization rates for AMI are reported to be 242 per 100,000 people from 2003 to 2005. The in-hospital and 30-day AMI mortality rates, however, have declined over the past decade based on reports from several studies (Chen et al., 2010; Fihn et al., 2009; Roger et al., 2012).

From the above statistics it is evident that AMI is a common condition with high mortality and morbidity. Therefore clinical guidelines, based on evidence from clinical trials, recommend the use of statins, β-blockers, aspirin, and ACEI/ARBs for the management of patients with AMI (Smith et al., 2011) in addition to lifestyle changes. Between 1980 and 2000, increased use of evidence-based therapies were responsible for an approximate 47% of the decrease in deaths due to CVD, whereas ≈44% decrease was attributable to changes in lifestyle and environmental factors bringing about a change in the risk factors in the population (Ford et al., 2007).

Adherence to Secondary Prevention Therapies post-AMI

Many studies have documented non-adherence to secondary prevention therapies post-AMI. Almost a decade ago, Bradley et al. (2001) suggested that less than half of post-AMI patients received β-blockers at hospital discharge. A recent analysis conducted using administrative data in Ontario, Canada found that approximately 27% of all prescriptions are not filled within 7 days of hospital discharge after MI (Jackevius, et al., 2008). Specifically concerning cardiac medications, 8% of patients did not fill their prescription for beta-blockers and only 44% filled their antiplatelet prescription. Contemporary U.S. data provide similar findings (Fischer et al., 2011). This is an example of primary non-adherence (Rashid, 1982; Vermeire, Hearnshaw, Van

Royen, & Denekens, 2001) whereby the patient fails to fill the initial prescription at the start of therapy and is seen by some as a more severe form of non-adherence (Jackevius et al., 2008). Using data from commercial health plans, Lee et al. (2008) reported that of 1,135 members with Acute Coronary Syndrome (ACS, including unstable angina as well as AMI), 52% had at least 1 pharmacy claim for an ACEI/ARB, 64% for a β-blocker, 63% for a statin, and 30% for all three key drug classes, during the three month follow-up period. Among patients that started aspirin, statin and β-blocker therapies post-AMI, it was reported that about 34% stopped at least one medication and 12% stopped all three within 1 month of hospital discharge (Ho et al., 2006). The study used a prospective cohort design and medication discontinuation was determined using telephone interviews. Initiation of secondary prevention therapies post-AMI is still suboptimal as suggested by the above studies. However, a considerable increase in the use of β-blockers and ACEI over the years has been documented (Gislason et al., 2005; National Committee for Quality Assurance [NCQA], 2006; Rasmussen et al., 2005) with the publication of guidelines that advocate the extensive use of these agents post-AMI. Several organizations have also taken the initiative to increase prescribing of evidence-based medicine at hospital discharge associated with an AMI. These include the American College of Cardiology (ACC)'s Guidelines Applied in Practice (GAP), "Get with the Guidelines" by the AHA, the Joint Commission on Accreditation of Health Care Organizations (JCHO)'s quality check, and the National Committee for Quality Assurance (NCQA)'s Health Plan Employer Data and Information Set (HEDIS) (Labresh et al., 2004; Mehta et al., 2007; NCQA, 2003).

Even when patients fill their initial prescriptions post-AMI, data suggests that they have low rates of long-term persistence (Ackincigil et al., 2007; Butler et al., 2002; Frohnapple, & Mehta, 2002; Kramer et al., 2006; Lee et al., 2008; Mitra, Findley, Benner, Glynn, Mogun,

Neumann, Weinstein, & Avorn, 2002; Newby et al., 2006;). These studies, however, have used different methodologies and definitions of long-term persistence. Self-report of consistent use of cardiac medication over 6 to 12 months was low (Newby et al., 2006). Approximately three-fourths of the patients reported persistent aspirin use (71%), whereas less than half reported persistent use of β-blockers (46%), lipid-lowering agents (44%), and all three medications (21%) after diagnosis of coronary artery disease (CAD). Butler et al. (2002) analyzed prescription data of Tennessee Medicaid enrollees post a hospital discharge for AMI. If the subjects had not filled their prescription in the prior 30 days at 180 and 365 days post discharge, they were considered to have discontinued their prescriptions. The authors reported that 63% and 61% of patients who were discharged on β-blockers were current users at 180 and 365 days respectively. Mitra et al. (2002) analyzed clinical data over a 24 month follow-up period and found that the percentage of patients receiving aspirin, β-blockers, and ACEI had fallen to 88%, 71%, and 43%, respectively, whereas use of lipid-lowering agents slightly increased. When therapy discontinuation was defined as a lapse of 60 days or more after exhausting the cumulative days supplied from prior prescriptions, Akingicil et al. (2007) found that 32% of the AMI patients discontinued ACEI after a year and 50% at 2 years. The rates for β-blocker discontinuation were found to be similar. Their approach provides a more conservative definition of discontinuation that allows for error due to occasional use of medication samples or billing problems. On analyzing health plan records from members of 11 health plans, Kramer et al. (2006) reported that only 45% of the patients were adherent to β-blockers (defined as prescription claims covering $\geq$ 75% of days) for 360 days post discharge following an AMI. The biggest drop in adherence was between 30 and 90 days with participation in Medicare + Choice product, residence in the Southeast, and younger age being statistically significant predictors of lower adherence. Among Medicare

patients enrolled in a pharmacy benefit program only 42% were found to be adherent with their prescribed statins after 2 years (Benner et al., 2002). During 18 months of follow-up, Lee et al. (2008) reported that 65% of patients diagnosed with ACS had at least 1 pharmacy claim for an ACEI/ARB, 76% for a β-blocker, 77% for a statin, and 46% for all 3 medication classes. Looking at trends in adherence among elderly Medicare beneficiaries between 1995 and 2003, Choudhry, Setoguchi, Levin, Winkelmayer, and Shrank (2008) demonstrate a modest but statistically significant improvement in adherence to statins and β-blockers over time. However, the overall rates of adherence still remained suboptimal.

Non-adherence to secondary prevention therapies post-AMI has also received attention globally. A cohort study using administrative data from Ontario demonstrated that only an approximate 40% of 22,379 subjects were still taking statin prescriptions 2 years post discharge for ACS (Jackevicius, Mamdani, & Tu, 2002). Subjects were defined as continuing therapy if they had at least 1 claim for a statin prescription every 120 days after the index prescription date. Cardiac drugs were found to be under-prescribed to elderly patients with AMI using Quebec administrative data (Simpson, Beck, Richard, Eisenberg, & Pilote, 2003). However the results suggest that once prescribed, patients are likely to adhere to these with high rates of compliance and persistence over one year with 60-80% continuing treatment. In Denmark, Gislason et al. (2006) reported that after 5 years of treatment 58% of the survivors were still receiving β-blockers, with 74% and 82% still on ACEI and statins respectively. Therapy discontinuation was conceptualized as the first break of 90 days or longer. In Estonia, only 40% of the patients who suffered from AMI (n = 4,025) were treated by a combination of β-blockers, ACEI/ARBs and statins (Marandi, Baburin, & Ainla, 2010). Supporting the above results, Sorensen et al. (2008)

found substantial underuse of clopidogrel treatment in patients with MI without a percutaneous coronary intervention (PCI) using prescription claims in Denmark.

The above numbers are difficult to compare, as studies use varied definitions of adherence and persistence. Subjects are known to restart therapies even after a break of 90 days or more (Gislason et al., 2006). With this fact in mind, the corroborative results from the studies enlisted above still paint a dismal picture of the current state of the secondary prevention regimen post-AMI. A recently published meta-analysis of 20 studies (Naderi et al., 2012) assessing adherence to primary and secondary prevention therapies among patients of CVD reported a summary estimate of 57% of adherence across all studies after a median of 24 months. Patients were classified as adherent if they had at least 75% of days covered for a specific drug over a specified time period. The meta-analysis suggested that approximately one third of patients with a history of myocardial infarction do not adhere to secondary prevention therapies although the maintenance of these therapies indefinitely post-AMI has been recommended (Smith et al., 2011).

Association between Medication Adherence and Outcomes post-AMI

Several randomized trials since the mid-1980s and meta-analyses of those clinical trials (see Hennekens et al. [1996] for a review) have suggested that secondary prevention therapies post AMI improve survival and reduce the risk of reinfarction. The number of observational studies is comparatively fewer. Jackevius et al., 2008 reported that the 1-year mortality rate was higher (odds ratio [OR], 1.80; 95% confidence interval [CI] 1.15 to 1.79; $p<0.0001$) for patients who did not fill all of their recommended discharge medications within 120 days after the index date versus those who had filled none. Similarly, medication therapy discontinuation at 1 month was

also associated with higher 1-year mortality (hazard ratio [HR], 3.81; 95% CI 1.88 to 7.72) (Ho et al., 2006). In the Korea Acute Myocardial Infarction Registry, administration of all four recommended classes of prevention therapy at discharge was found to be an independent predictor of 6 month mortality using a Cox proportional hazards model (Lee et al., 2010). The above studies have explored the relationship between administration of secondary prevention therapies at discharge and outcomes.

In contrast to this, a number of studies have reported estimates of the effects of long-term adherence or persistence to one or all of the recommended drug classes on outcomes such as recurrent MI and mortality. Self-report of consistent use of aspirin, β-blockers, lipid-lowering therapy over 6 to 12 months was associated with lower adjusted mortality over the seven year study period (Newby et al., 2006). Wei et al. (2002) report an adjusted relative risk of recurrent MI of 0.19 (95% CI 0.08 to 0.47) and all-cause mortality of 0.47 (95% CI 0.22 to 0.99) for those who had 80% or better adherence to statins, compared with those not taking statins. The study was conducted using 5 years of administrative data in Scotland and adherence to statins was computed beginning the occurrence of the first AMI to the end of the study period. Amin et al. (2009) studied the association of non-compliance with evidence based medical therapies after AMI on death and recurrent MI in a population that comprised of greater than 80% minority race groups and greater than 70% uninsured. Non-compliance with ≥4 evidence-based medications was an independent factor associated with death or recurrent MI (HR, 2.83; 95% CI 1.60 to 5.01). Rasmussen et al. (2007) categorized adherence to statins, β-blockers and calcium channel blockers (CCBs) computed over a year post discharge into 3 categories – high (PDC, ≥80%), intermediate (PDC, 40%-79%), and low (PDC, <40%). They report a dose-response type adherence-mortality association for statin and β-blocker users, where compared to their high

adherence counterparts, the risk of mortality was greatest for low adherers and intermediary for intermediate adherers. Long-term mortality was assessed till the last available follow-up date (median, 2.4 years). Similarly, good adherence i.e. >80% to β-blockers computed over a year post discharge following AMI, was associated with a lower adjusted relative risk (RR) of mortality (RR, 0.49; 95% CI 0.30 to 0.80) compared with patients not on the therapy over four years of follow-up (Wei, Flynn, Murray, & MacDonald, 2004). Non-persistence, defined as a break in therapy of 90 days or more, with β-blockers (HR, 1.25; 95% CI 1.19 to 1.32) and statins (HR, 1.88; 95% CI 1.67 to 2.12) was also associated with increased mortality (Gislason et al., 2007). Shaya, Gu and Yan (2008) reported an increased likelihood of re-infarction (HR, 1.66; 95% CI 1.03-2.69) among patients that discontinued statins, β-blockers or calcium channel blockers after and AMI. A patient was classified as non-persistent if the refill gap exceeded three times the day supply of the previous prescription.

There have been very few studies (Ho et al., 2008; Levy et al., 2004) that have measured adherence to secondary prevention therapies as a time-varying predictor while estimating its association with cardiovascular outcomes or all-cause mortality. Ho et al. (2008) computed adherence to statins, ACEIs, and β-blockers for each 180-day interval among patients with Coronary Artery Disease (CAD), identified using the Kaiser Permanente of Colorado's database. The median follow-up was 4.1 years. Non-adherence to each of the 3 classes of drugs was found to be common and remained significantly associated with higher risk of all-cause mortality, cardiovascular mortality, cardiovascular hospitalization, and revascularization procedures. Cox proportional hazards models with a time-varying covariate for medication non-adherence was used for analysis. Using a similar analytic model and a time-dependent measure of β-blocker use, the risk of dying during periods of β-blocker use was found to be attenuated (HR, 0.6; 95%

CI 0.5 to 0.7) when compared to the risk of dying when the drug was not available (Levy et al., 2004). The authors operationalized drug exposure by creating a drug-by-day matrix where β-blocker use for each day for each subject was represented by a binary variable.

Delaney et al. (2009) compared the estimates for the effect of β-blocker use post-AMI on all-cause mortality over a 9 month follow-up period from a marginal structural model (MSM) and traditional regression model. Patients' blood pressure was used as the time varying confounder and β-blocker use post AMI was defined as the presence of at least 1 β-blocker prescription in the 90days post-AMI. A protective effect of post-AMI β-blocker use was found using both models. The estimate from the MSM however, was found to be closer to that derived from a meta-analysis of RCTs, while that from the traditional model overestimated the effectiveness.

Marginal Structural Models (MSMs)

MSMs were proposed around a decade ago (Robins, 1999; Robins et al. 2000) to account for time-dependent confounding. Some studies that have employed this technique have reported differences in estimates with MSMs and those obtained by traditional methods (Hernan, et al., 2000; Bodnar, et al., 2004; Teng et al., 2005; Cole, et al., 2005). They all recommend the use of MSMs in the presence of time-dependent confounding.

Hernan et al. (2000) used MSMs to estimate the causal effect of zidovudine on the survival of human immune-deficiency virus (HIV) positive men. CD4 lymphocyte count was modeled as the time-dependent confounder. After controlling for baseline covariates, the standard survival analysis methods yielded a decrease in the mortality rate ratio to 1.7 (95% CI 1.4 to 1.9) from a crude estimate of 2.3 (95% CI 2.0 to 2.7). However, on using MSMs to

account for time-dependent confounding the mortality rate ratio was found to be 0.7. (95% CI 0.6 to 0.9). Bodnar et al. (2004) describe the application of MSMs to estimate the causal effect of iron supplementation during pregnancy on the odds of anemia at delivery. On accounting for time-dependent confounding they observed a reduction in the odds of anemia by 93% associated with the treatment, whereas, ordinary logistic regression models suggested a 4.3 fold increase in the odds. Similarly, the 2-year survival benefit associated with injectable vitamin D among hemodialysis patients was found to be 20% using Cox proportional hazard analysis with time-varying treatment, and 26% using MSMs. Yu et al. (2010) estimated the effects of medication adherence to hypoglycemics on the risk of micro vascular complications in type 2 diabetes patients. The Cox models with time-invariant and time-varying adherence measures, and after accounting for time-varying covariates, presented a detrimental effect of higher adherence. The estimates from MSM, however, suggested that higher medication adherence may results in a reduced risk of micro vascular complications among patients with type 2 diabetes.

The estimates of the effect of physical activity on COPD development obtained using MSMs and standard approaches were not found to be different (Garcia-Aymerich, Lange, Serra, Schnohr, & Anto, 2008). The authors conclude that time-dependent confounding may have not played a significant role in this relationship. They also suggest that publication bias could be another issue, as studies that do not find differences between standard methods and MSMs probably do not get published. It is important to make a note of this issue. However, they also acknowledge the fact that they may have misspecified the model.

Considering the above, this study aims to explore the differences between estimates obtained from several traditional methods and MSMs using the same study population. As mentioned earlier, it is very likely that studies that do not show benefits of the MSM

methodology over conventional methods do not get published. In addition to the model specification, previous studies have also taken varied approaches as far as the measurement of adherence is concerned while estimating the effect of adherence on outcomes.

Measuring Medication Adherence

The terms adherence, compliance and persistence are commonly used and often inappropriately interchanged. On conducting a comprehensive literature review the Medication and Compliance Special Interest Group of ISPOR, the International Society for Pharmacoeconomics and Outcomes Research (Cramer et al., 2007) proposed two different and distinct concepts to use while studying medication behavior. Adherence to (or compliance with) a medication regimen was defined as the 'extent to which a patient acts in accordance with the prescribed interval and dose of a dosing regimen'. There is a subtle difference between the two terms 'adherence' and 'compliance'. The term 'compliance' suggests that the patient is passively following the doctor's orders and is not involved in shared decision-making with the physician as far as his/her therapeutic regimen is concerned (Osterberg, & Blaschke, 2005). However, when measured using observational data, they are essentially synonymous. Medication 'persistence' was defined as 'the duration of time from initiation to discontinuation of therapy' (Cramer et al., 2007).

There are many different methods of assessing medication adherence. These have been broadly categorized as direct and indirect (Osterberg, & Blaschke, 2005). As suggested by Osterberg, and Blaschke (2005) direct methods involve direct observation and/or directly measuring the level of the drug, metabolite or biological marker in the blood stream after administration. Although these methods are considered more robust, they have a few limitations, the most significant of which is that they are neither practical nor economical. Indirect methods

of measuring adherence include but are not limited to self-reports, pill counts, questionnaires, electronic medication monitors, patients diaries, and use of pharmacy claims data (Ellis, Shumaker, Sieber, & Rand, 2000; Osterberg, & Blaschke, 2005; Vermiere et al. 2001). Each of these methods has their own drawbacks and advantages.

The use of pharmacy claims data to measure adherence is widespread and has been associated with a broad range of outcomes in various different medical conditions (Ho et al., 2008; Simpson et al., 2006). Several measures of adherence using pharmacy data have been proposed over the years. Hess, Raebel, Conner, & Malone (2006) compared 11 of these measures: Continuous Measure of Medication Acquisition (CMA), Continuous Multiple Interval Measure of Oversupply (CMOS), Medication Possession Ratio (MPR), Medication Refill Adherence (MRA), Continuous Measure of Medication Gaps (CMG), Continuous Single Interval Measure of Medication Acquisition (CSA), Proportion of Days Covered (PDC), Refill Compliance Rate (RCR), Medication Possession Ratio, modified (MPRm), Dates Between Fills Adherence Rate (DBR), and Compliance Rate (CR). The two most commonly used adherence measures in observational studies include MPR and PDC (Ho, Bryson, & Rumsfeld, 2009; Martin et al., 2009). MPR is essentially defined by dividing the total days supply for the considered medication(s) during a set period of time by the pre-defined period of time (Steiner, & Prochazka, 1997). It has been consistently used to study medication adherence patterns and has been reported as one of the best predictors of subsequent outcomes for simple drug users (Hess et al., 2006; Karve, & Martin, 2007; Karve et al., 2008). A variation in the measurement of MPR is seen across studies with some researchers using the last refill while computing the numerator (Andrade, Kahler, Frech, & Chan, 2006; Hamilton, & Briceland, 1992), whereas others exclude it (Andrade et al., 2006; Bramley, Gerbino, Nightingale, & Frech-Tamas, 2006).

It has been used as a continuous variable or categorical variable (≥ 80% high, 40%-79% medium, < 40% low) (Andrade et al. 2006; Bramley et al., 2006; Hamilton, & Briceland, 1992; Rasmussen et al., 2007). PDC has been conceptualized as the proportion of days the patient has the medication over a pre-defined interval of time (Benner et al., 2002). It is indicative of days of overlap as well as gaps in therapy as the method to compute it requires each day of medication coverage to be flagged using a binary indicator. The resulting proportion is similar to MPR; however, it can be different when computing compliance for a class of medications where individuals take multiple drugs from the same class, simultaneously. Simply summing up the days supply while using MPR, will overestimate the adherence for that class of drugs (Martin et al., 2009). Using multiple drugs from the same class, simultaneously, would not lead to an increase in the drug count using PDC. Thus, the main difference between these 2 measures is that although the PDC varies between 0 and 1, the MPR can be ≥1 (Andrade et al., 2006; Hess et al. 2006; Ho et al., 2009; Steiner, & Prochazka, 1997); however, it is often truncated to 1 (Cantrell, Eady, Shah, Regan, & Sokol, 2006; Keene, Eady, Nelson, & Sarnes, 2005). Even while measuring adherence over shorter intervals of time using one adherence measure over another may make a difference. Using MPR in such scenarios will overestimate the adherence during one period of time, say 3 months, and underestimate it in the consecutive 3 month window if the patient pre-fills his/her claim before the start of the second 3 month period.

Three other alternatives that have been proposed in the same group of measures are MEDSUM, MEDOUT (Steiner, Koepsell, Fihn, & Inui, 1988) and ReComp (Bryson, Au, Young, McDonnell, & Fihn, 2007). MEDSUM is essentially the same as MPR and is calculated as (quantity of pills dispensed)/(pills per dose × doses per day)/(days in interval). MEDOUT represents the proportion of days the patient does not have the drug available. Refill Compliance

(ReComp) is a validated algorithm recently proposed by Bryson et al. (2007) and has been shown to be better suited when adherence is measured over shorter observation intervals repeatedly. In their analysis, ReComp yielded a better R^2 than MEDOUT and MEDSUM for shorter intervals, in all three different medication adherence-outcomes models. The measure is computed in a manner similar to PDC, however, over supply from previous periods is accounted for, which is not the case with PDC (Martin et al., 2009). The ReComp measure has been used successfully in other studies since it was initially proposed (Lambert-Kerzner et al., 2012; Thorpe, Bryson, Maciejewski, & Bosworth, 2009; Wang, Liu, Bryson, Sharp, & Maciejewski, 2011). The details of computing ReComp have been elaborated upon in the methods section.

Specific Aims and Hypotheses

In order to meet the specific aims listed previously, this study tested the following sets of hypotheses based on the literature:

Aim 1: To explore the predictors of patient adherence to secondary prevention therapies post-AMI.

H_{1a}: Age, gender, ethnicity, geographic region, Charlson comorbidity index (CCI), length of hospital stay, type of surgical procedure, other comorbid conditions and concomitant therapy are predictors of adherence to statin therapy post-AMI.

H_{1b}: Age, gender, ethnicity, geographic region, CCI, length of hospital stay, type of surgical procedure, other comorbid conditions and concomitant therapy are predictors of adherence to β-blocker therapy post-AMI.

H_{1c}: Age, gender, ethnicity, geographic region, CCI, length of hospital stay, type of surgical procedure, other comorbid conditions and concomitant therapy are predictors of adherence to angiotensin converting enzyme inhibitor (ACEI)/ angiotensin receptor blocker (ARB) therapy post-AMI.

Aim 2: To explore the relationship between adherence to secondary prevention therapies post-AMI measured as a time-invariant variable and the risk of subsequent outcomes.

H_{2a}: Patients that are more adherent to statin therapy post-AMI measured as a time-invariant predictor, are at a lower risk of suffering a i) recurrent AMI and ii) mortality compared to those who are less adherent, after adjusting for additional covariates.

H_{2b}: Patients that are more adherent to β-blocker therapy post-AMI measured as a time-invariant predictor, are at a lower risk of suffering a i) recurrent AMI and ii) mortality compared to those who are less adherent, after adjusting for additional covariates.

H_{2c}: Patients that are more adherent to ACEI/ARB therapy post-AMI measured as a time-invariant predictor, are at a lower risk of suffering a i) recurrent AMI and ii) mortality compared to those who are less adherent, after adjusting for additional covariates.

Aim 3: To explore the relationship between adherence to secondary prevention therapies post-AMI measured as a time-varying variable and the risk of subsequent outcomes.

H_{3a}: Patients that are more adherent to statin therapy post-AMI measured as a time-varying predictor, are at a lower risk of suffering a i) recurrent AMI and ii) mortality compared to those who are less adherent, after adjusting for additional covariates.

H_{3b}: Patients that are more adherent to β-blocker therapy post-AMI measured as a time-varying predictor, are at a lower risk of suffering a i) recurrent AMI and ii) mortality compared to those who are less adherent, after adjusting for additional covariates.

H_{3c}: Patients that are more adherent to ACEI/ARB therapy post-AMI measured as a time-varying predictor, are at a lower risk of suffering a i) recurrent AMI and ii) mortality compared to those who are less adherent, after adjusting for additional covariates.

Aim 4: To compare predictive values of adherence measured as a time-varying and time-invariant variable in assessing the risk of subsequent outcomes.

$H_{4a:}$ The time-varying measure of adherence to statin therapy post-AMI is superior to the time-invariant measure in predicting subsequent outcomes, after adjusting for additional covariates.

$H_{4b:}$ The time-varying measure of adherence to β-blocker therapy post-AMI is superior to the time-invariant measure in predicting subsequent outcomes, after adjusting for additional covariates.

$H_{4c:}$ The time-varying measure of adherence to ACEI/ARB therapy post-AMI is superior to the time-invariant measure in predicting subsequent outcomes, after adjusting for additional covariates.

CHAPTER 3

METHODOLOGY

The broad purpose of this study was to explore the effect of long-term adherence to secondary prevention therapies post-AMI on subsequent cardiovascular events using time-constant and time-varying measures of adherence. To achieve this, a longitudinal cohort observational study design was employed using the retrospective Medicare 5% random national sample claims data from January 1st, 2006 to December 31st, 2008. Data for the study were obtained from the Centers for Medicare and Medicaid Services (CMS) via a Data Use Agreement (DUA) outlining the specifics of the study protocol. Additionally, the study was approved by the Institutional Review Board (IRB) at The University of Mississippi.

Data Source

Medicare is a national social program, administered by the U.S. federal government since 1965. It provides access to health insurance coverage for elderly U.S. citizens aged 65 years and older, as well as younger individuals with disabilities and end stage renal disease (ESRD). The program has four parts. Part A covers hospital care, Part B covers outpatient medical services, and Part D covers outpatient prescription drugs. Medicare Advantage, also known as Medicare Part C is another option provided by the federal government for beneficiaries to receive their Part A and B benefits through private health insurance, and hence is also known as Medicare +

Choice plan. A 5 % random national sample of the Medicare claims data is available for research purposes through the CMS and was used for analysis purposes.

The following Research Identifiable Files (RIFs) for 2006-2008 were requested; the Master Beneficiary Summary File, the Carrier RIF, the Outpatient RIF, the MedPAR RIF, and the Part D Drug Event (PDE) File. The Master Beneficiary Summary File includes person-level data and comprises of several segments. Of these, the Medicare Enrollment segment contains data on the beneficiaries' enrollment status, demographics, and managed care and part D enrollment indicators. The Carrier RIF also known as the Physician/Supplier Part B claims file includes claim-level information from non-institutional providers i.e. physicians, physician assistants, nurse practitioners, and so on. The file contains data on diagnosis and procedure codes, dates of service, reimbursement amounts, and provider numbers. The Outpatient RIF contains claim-level data similar to the Carrier file, except the claims submitted are from institutional outpatient providers such as hospital outpatient departments, rural health clinics, renal dialysis facilities, outpatient rehabilitation facilities, community mental health centers and so on. Each record on the MedPAR RIF represents an inpatient hospital or skilled nursing facility (SNF) stay and may represent multiple claims from the beneficiary's stay for that event. The variables in the dataset are similar to the ones in the Carrier and Outpatient files. The PDE data contains prescription claim information such as National Drug Codes (NDCs), days supply, date of service, and drug costs. The records in these files can be linked to each other using the encrypted beneficiary identification code, which allows one to identify and analyze health care utilization data for a particular beneficiary over several years (http://www.resdac.org/cms-data/file-family/Medicare-Claims).

Rationale for use of Medicare 5% random national sample data. The Medicare 5% data was found to be appropriate for analysis purposes due to several reasons. Firstly, the algorithm that was used to identify patients with an initial episode of AMI was validated using Medicare data and reported to have a 94.1% (95% CI, 93.0% - 95.2%) predictive validity (Kiyota et al., 2004). The authors conclude that discharge diagnosis codes in Medicare claims data for AMI are highly accurate and suitable for use in epidemiologic studies. Identification of the target population accurately is a key question in any claims-based study and this reduces the error due to misclassification greatly. Additionally, the data has a nationally representative sample which extends the generalizability of the results. A possible limitation of using the data could be that the study population comprised of elderly individuals ≥65 years of age. According to Heart Disease and Stroke Statistics-2012 update the average age at first AMI is 64.5 years for men and 70.3 years for women (Roger et al., 2012); therefore studying this population can be justified. However, the association between adherence and outcomes in this population may not be representative of a younger population, and hence results should be interpreted cautiously. The statistics also report that among patients aged ≥65 years at initial AMI approximately 25% have a recurrent MI within 5 years and ≈28% die within a year. This implies that with a sufficiently large sample size the frequency of event occurrence should be sufficient for statistical techniques that have been used later on. A major drawback was the unavailability of data on certain crucial risk factors, such as smoking. However, this information is not available in most claims data that would be required for the study purpose.

Study Design and Study Population

The Medicare 5% random national sample files from January 1, 2006 through December 31, 2008 were analyzed (Figure II). Service claims from July 1, 2006 through June 30, 2007 were

used to identify patients with an initial episode of AMI using an identification algorithm validated by Kiyota et al. (2004). As per the algorithm, a hospitalization episode lasting at least 3 days and ≤180 days with an International Classification of Diseases, Ninth Revision, Clinical

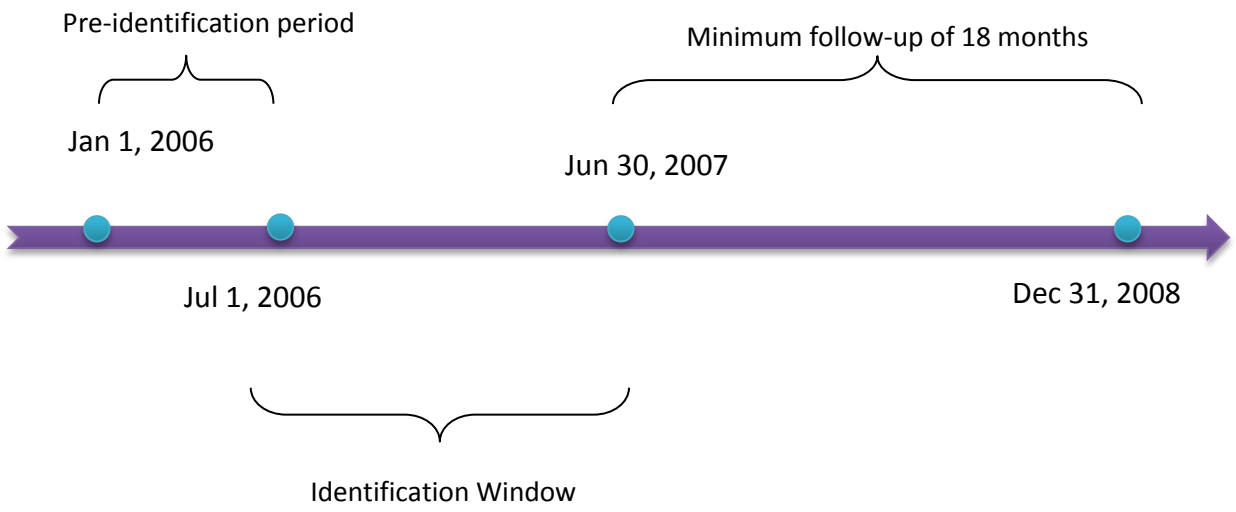

Figure II Graphical representation of study design

Modification (ICD-9-CM) diagnosis code of 410.*x*1 (*x* = 0 to 9) in the primary or secondary diagnosis position was used to identify an episode of AMI. The date of discharge following the initial hospitalization episode of AMI was used as the index date for subjects. Re-admission within 8 weeks for a subsequent episode of care related to the initial AMI has an ICD-9-CM diagnosis code of 410.*x*2 and an old episode of AMI has an ICD-9-CM diagnosis code of 412.*xx*. Therefore, patients with an ICD-9-CM diagnosis code of 410.*x*2 or 412.*xx* listed as any of the diagnoses codes for a hospitalization episode that occured before the index date were excluded from the study. Further, occasionally, in some claims related to a hospitalization episode due to AMI the fifth digit in the ICD-9-CM diagnosis code is populated as zero (i.e. 410.*x*0), which represents an unspecified episode of care. These patients were included in the study and their medical claim records before the index date were analyzed to ensure the inclusion of only those

with an initial episode of care. It is precisely for this reason that the study design includes a pre-index period from January 1, 2006 to June 30, 2006. This pre-identification period was used to analyze the claims history of patients included in the study earlier on during the identification window and to gain information on baseline comorbidities (elaborated upon later). Similarly, the study design allows for a minimum 18 month follow-up period (upto December 31, 2008) after the identification window to ensure sufficient time to study the adherence-outcome relationship among patients with an index date towards the end of the identification window. Studies have shown that adherence to treatment starts declining after 2 years (Akincigil et al., 2007).

After identification of initial AMI episodes, only patients that did not have a recurrent AMI for the first 90 days and survived the first 90 days were included in the study. These patients probably have a more severe disease burden and have other factors associated with the outcome, such as use of drug post discharge rather than adherence. Since the objective of the study is to determine the association between long-term adherence and outcomes, this exclusion criterion is justified. Selected beneficiaries were required to have continuous enrollment in Medicare Parts A, B, & D, from 6 months before to 12 months after the index date, or up until their death date if they died within a year. Continuous enrollment 6 month prior to the index date was required to obtain prior medication history. Continuous enrollment 12 months after the index date enabled acquiring sufficient adherence data before the subject was censored. Continuous enrollment throughout the study period was not opted for as it may lead to a reduction in sample size. Instead, censoring patients at the end of 12 months post the index date in case of disenrollment led to additional data points that were used for the analysis. Further, patients enrolled in Medicare due to disabilities and/or ESRD were excluded, and those with

claims for SNF during the study period were excluded as their prescription claims may not be present.

Following their inclusion as described above, AMI patients that initiated statin therapy within 90 days post-discharge were included in cohort A. Similarly, those that initiated β-blocker therapy within 90 days post-discharge were included in cohort B. However, β-blockers are contraindicated in patients with asthma (Smith et al., 2011; Himmelstein, Woolhandler, Hellander, & Wolfe, 1999); therefore subjects that filled a prescription for inhaled corticosteroids or had an asthma diagnosis in their claims in the previous 6 months were excluded from cohort B. Additionally, patients with hypotension, sinus bradycardia and partial AV block (see Appendix A, Table XIX for ICD-9-CM diagnosis and procedure codes) were also excluded from this cohort using diagnosis codes from previous claims. Further, chronic obstructive pulmonary disease and insulin-dependent diabetes mellitus are relative rather than absolute contraindications, patients with these conditions were not excluded, but these conditions were controlled for. Finally, patients that initiated ACEI/ARB therapy within 90 days post-discharge constituted cohort C. NDC codes were used to identify prescription drug claims to create the 3 cohorts (refer to Appendix B for list of drugs that were considered). Sample attrition details are provided in Table I.

The selected patient cohort was followed until the first occurrence of any one of the following events: 1) disenrollment from Medicare Parts A, B, or D, 2) occurrence of the outcome, and 3) the end of the study period (31st December, 2008).

Table I Sample Attrition

	Inclusion/exclusion criteria	N
1	Subjects with Initial AMI between Jul 1, 2006 and Jun 30, 2007 identified using a valid algorithm	15,840
2	Excluding subjects enrolled due to ESRD and/or other disabilities	13,753
3	Excluding subjects with HMO coverage at any time during study period	12,569
4	Subjects with continuous enrollment in Medicare parts A/B and D 6 months prior and 12 months post index date or up to death date (whichever comes first)	5,445
5	Excluding subjects with skilled nursing facility (SNF) claims any time during the study period	2,933
6	Excluding subjects with previous AMI claims	2,555
7	Excluding subjects that died within 90 days of hospital discharge	1,698
8	Excluding subjects with a recurrent MI in the first 90 days post discharge	1,549
9a	Patients that initiated statin therapy within 90 days post-discharge (cohort A)	1,091
9b	Patients that initiated β-blocker therapy within 90 days post-discharge (cohort B)	1,021
9c	Patients that initiated ACEI/ARB therapy within 90 days post-discharge (cohort A)	1,025

Adherence Measurement

For each class of drugs the ReComp measure was used to compute adherence over 1 year as a time-constant measure and over 90-day intervals as time-varying. If a patient died within the interval, adherence beginning the first day of the interval to the death date was computed. The algorithm for the measure has been validated and recommended for use while measuring adherence over short intervals of time, repeatedly (Bryson et al., 2007). Hence, it was preferred for use in this study.

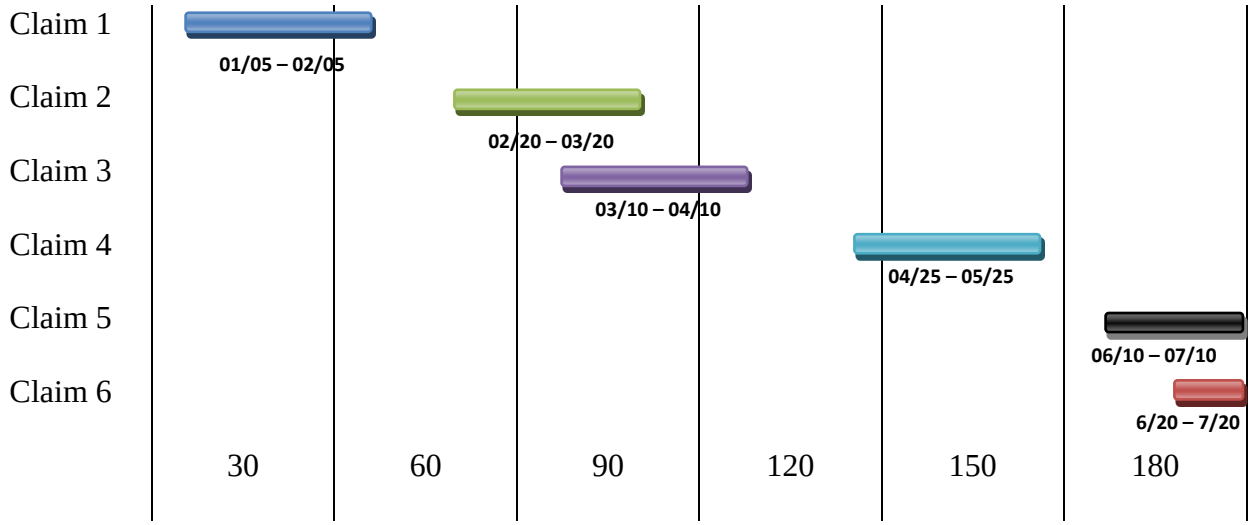

Figure III Graphical illustration of a prescription refill pattern

Consider a patient with prescription claim history as illustrated in Figure III above. The adherence measure for the first 90-day interval will be computed as ([30+30+10])/90 i.e. 0.78. If one would use the MPR measure and sum the days supply within the specified interval, the adherence would be 1. On using the PDC, the adherence for the first 90-day interval would be computed as 0.78, which is similar to the ReComp measure. However, oversupply is not accounted for while computing the PDC (Martin et al., 2009) and hence the difference would arise in the second 90-day interval. Here the PDC measure would be ([30+20]/90) i.e. 0.56. Taking into account the additional 20 days where the patient had the medication due to pre-fill in the previous 90 day interval, the ReComp measure of adherence would be 0.78.

Briefly, the MPR would overestimate the adherence in some intervals, while underestimating it in others. The PDC would underestimate adherence in intervals following a pre-fill in the previous one. Thus, the ReComp was found to be best suited for this study design.

Study Variables

Adherence. Adherence to statins, β-blockers and ACEI/ARBS was computed as described above. The time-varying measure was computed over each 90 day interval, beginning the index date, and up until the last date the subject was still in the study as per the study design. A 90-day interval was considered suitable as certain refills are for a 90 day supply, thus, shorter intervals would not work. Time periods greater than 90 days would not capture the truly dynamic nature of adherence. The time-constant measure was computed over a 1-year period post-index date. While computing adherence to a particular class of medications, say statins, medication switching from one drug to another in the same class of drugs was not classified as discontinuation of drug therapy. Consequently, patients who switch from ACEIs to ARBs or vice versa were considered as still continuing therapy. The adherence level over the period under consideration was dichotomized using the 80% value. Thus, subjects with an adherence of ≥80% were considered adherent for that particular period and those below 80% were classified as non-adherent. Although the dichotomous cutoff is arbitrary, it has been used for a majority of the studies on medication adherence in the literature (Claxton, Cramer & Pierce, 2001; DiMatteo et al., 2002; DiMatteo, 2004). The 80% cutoff may be too low for certain classes of medications such as oral contraceptives or human immunodeficiency virus; however, it seems reasonable for cardiovascular medications (Bryson et al., 2007; Ho et al., 2009). A dichotomous variable was preferred over a continuous measure due to the ease of interpretation of the final hazard ratios the former offers over the latter. Additionally, sensitivity analyses with various cutoff points between 40% and 90% were also conducted to substantiate the conclusion.

Baseline covariates. Socio-demographic variables such as age, gender, ethnicity, and region of U.S. were included as baseline covariates. These have been shown to be predictors of adherence

among varied classes of chronic medications in numerous studies (Gislason et al., 2006; Gislason et al., 2007; Rasmussen et al., 2007). Age in years at the index date was categorized as 65-70 years, 71-75 years, 76-80 years, 81-85 years, and 85+ years. Gender was classified into male and female. Ethnicity was categorized as White, Black, and other. Regions of the U.S. was grouped into Northeast, Midwest, South and West as per the United States Census Bureau (http://www.census.gov/geo/www/us_regdiv.pdf) using the state codes in the demographic file. The Charlson Comorbidity Index (CCI) measured over the 6-month pre-index period was used as an indicator of the baseline clinical condition of the patient (D'Hoore, Bouckaert, & Tilquin, 1996). The length of hospital stay classified as <7 days and ≥7 days was used as a measure of the severity of the patient's condition. If the patient received percutaneous coronary intervention (PCI) during the hospital stay it was indicated using a dichotomous variable. Similarly, an indication of treatment with coronary artery bypass graft (CABG) surgery during hospital stay was used as a baseline covariate (see Appendix A, Table XIX for ICD-9-CM procedure codes). The presence of angina and coronary artery disease, as dichotomous variables, prior to the initial AMI hospitalization were also computed. In addition to these, in patients on β-blocker therapy (cohort B) prior COPD was controlled for (see Appendix A, Table XIX for ICD-9-CM diagnosis codes). Dichotomous variables were also used to indicate prior use of statin, β-blocker, and ACEI/ARB therapy, respectively.

Time-varying confounders. The time-varying confounders were measured over each 90-day interval, beginning the index date, till the last day of follow-up for each subject. Number of office/outpatient visits was measured as a count variable. Any hospitalization visit and any ER visit were accounted for as dichotomous variables. Presence of revascularization procedures such as PCI and CABG were accounted for dichotomously. The presence of any diagnosis

related to conditions recognized as risk factors for secondary AMI were controlled for. These include hypertension, diabetes, dyslipidemia, congestive heart failure, cerebrovascular disease, and peripheral vascular disease (see Appendix A, Table XIX for ICD-9-CM diagnosis codes). In addition to these, another variable indicated the presence of any diagnosis related conditions that have a very low survival rate. These included chronic kidney disease and cancer. The number of drugs with unique active ingredients in every 90-day interval was also computed. Additional HMO coverage and Medicare Part D donut hole status for every quarter was controlled for. Total out-of-pocket Medicare cost for enrollees for every quarter was also included as a time-varying predictor.

In addition to the above time-varying confounders, for cohort A, where the effect of long-term adherence to statins on outcomes was investigated, adherence to β-blockers and adherence to ACEI/ARBs was also included as time-varying confounders. Similarly, when adherence to β-blockers or adherence to ACE/ARBs is the primary variable of interest, adherence to the other two classes under consideration was included as a time-varying confounder. However, in cases where the individual is not taking one or both of the other drug classes, the adherence was not zero, but rather indicated as 'drug not taken'. Therefore, when adherence was modeled as a time-varying confounder it was not a dichotomous variable, but had three levels representing adherence ≥80%, <80% and absence of drug, respectively.

Finally, in analysis models where the outcome variable is time to mortality the occurrence of subsequent AMI episodes was included as a dichotomous time-varying covariate.

Outcomes. Two outcome variables were studied. The first outcome was defined as time from the index date to the occurrence of the first episode of a recurrent AMI. Similarly, the time to

mortality from the index date was the second outcome. Time in this case will be measured in discrete intervals (90 days) or continuously (daily) depending on the statistical model used. This has been elaborated upon later.

Data Analysis

The data management and the data analysis for the study were conducted using Statistical Analysis Software (SAS) version 9.3. The baseline descriptive characteristics for all subjects have been reported using means and standard deviations for continuous variables, and number and percentages for categorical variables. Additional descriptives of the data such as the average and median quarters of follow up as well as the average number of subjects adherent to each class of drug during each quarter have been provided. The data analysis plan for each of the specific aims is discussed below.

Aim 1: To explore the predictors of patient adherence to secondary prevention therapies post-AMI.

To examine predictors of adherence to statin therapy, multivariable logistic regression models were used. The time-invariant, dichotomous, 1-year adherence measure was used as the dependent variable with all the baseline covariates included in the model. Similar, multivariable logistic regression models were used to examine predictors of adherence to β-blocker therapy and ACEI/ARB therapy.

Aim 2: To explore the relationship between adherence to secondary prevention therapies post-AMI measured as a time-invariant variable and the risk of subsequent outcomes.

The Cox proportional hazard models (Cox, 1972) were used to estimate the effect of adherence on the risk of subsequent outcomes. The model provides a semi-parametric regression technique

to estimate the risk associated with the occurrence of events at specific intervals of time due to certain factors. The basic model is usually represented as,

$$h_i(t) = \lambda_0(t)exp\left(\beta_1 X_{1\,ij} + \ldots\ldots + \beta_k X_{k\,ij}\right) \quad \ldots\ldots(1)$$

which suggests that the hazard for an individual *i* at time *t* is a product of the baseline hazard function and the exponentiated linear function of a set of *k* covariates. Around 10-20 variables per event have been suggested for the generation of accurate estimates (Concato et al., 1995; Peduzzi, Concato, Feinstein, & Holford, 1995).

The model was estimated using the time-invariant dichotomous measure of adherence to statins (using cohort A) as the primary predictor variable with time to recurrent AMI and time to mortality as the dependent variable, respectively. Baseline covariates were adjusted for. Additionally, the presence of concomitant therapy with β-blockers and ACEI/ARBs were also adjusted for.

Similar analyses were conducted using adherence to β-blocker (using cohort B) and ACEI/ARB (using cohort C) therapy as primary variables of interest, respectively.

Aim 3: To explore the relationship between adherence to secondary prevention therapies post-AMI measured as a time-varying variable and the risk of subsequent outcomes.

In order to achieve the above purpose, 3 different modeling strategies were constructed with varying specifications. Model 1 included the baseline covariates and time-varying adherence. Model 2 included the baseline covariates, time-varying covariates and time-varying adherence; however, the dynamic interactions between the covariates and adherence measures are ignored in this model. Lastly Model 3 was a MSM which included the baseline covariates, time-varying

covariates and time-varying adherence and also accounted for the effect of time-dependent confounding. All of the above models were used to generate estimates of the effects of adherence to each of the 3 drug classes under consideration on each of the 2 outcomes discussed earlier.

Discrete-event time models (models 1 and 2). In this case the time dependent covariates were measured at regular intervals of 90 days i.e. quarterly which do not correspond to the units in which the event times were measured i.e. days. A Cox proportional hazard model with time-varying predictors cannot be directly used with this data. Singer and Willet (2003) have suggested 3 ways of dealing with this situation: 1) to impute predicted values for the intermediate event times, 2) to disregard time-varying predictors completely, and 3) to round the event times so as to reflect the time-intervals over which the predictors are measured. Option 1 does not seem feasible as the study includes several time-dependent variables for a large sample size and their values will be required to be imputed for each day of follow up. Disregarding the time-varying predictors would mean ignoring valuable information, thus option 2 was not opted for[1]. Therefore, the occurrence of the event i.e. recurrent AMI or mortality over the 90-day interval was used as the outcome variable.

Now, since the occurrence of the event is being measured at discrete intervals (quarterly) rather than continuously (daily), Cox's model for discrete-event time data, with a complementary log-log (clog-log) link, was used for analysis (model 1 and model 2). The model is represented as follows:

[1] Prior studies (Ho et al., 2008; Levy et al., 2004; Yu et al. 2010) that have measured adherence as a time-varying variable have used continuous time models to estimate the effect of adherence on outcomes. Therefore in order to be able to compare our results, findings from continuous time models (models 1b and 2b) have also been reported in Appendix C – Additional Results.

$$clog - log\ h(t_{ij}) = \ [\alpha_1 D_{1\,ij} + \alpha_2 D_{2\,ij} + \cdots + \alpha_J D_{J\,ij}] +$$

$$[\beta_1 X_{1\,ij} + \beta_2 X_{2\,ij}\ \ldots\ldots + \beta_P X_{P\,ij}] \ldots\ldots\ldots\ldots\ldots\ldots\ldots (2)$$

On the right side of equation 2, the first set of parameters, as a group, represent the baseline clog-log hazard function i.e. the value of the clog-log hazard when all the P substantive predictors are 0. The second set, as a group, represents the shift in the baseline clog-log hazard function corresponding to unit changes in the predictors. If one of the predictors, say X_2 was time-varying, then individual i's value of clog-log hazard in time *j* depends on his value of X_1, X_3,… X_P, which is time-invariant, and his value of X_2 in time *j*.

The left-side of equation 2 uses a clog-log transformation. It yields the logarithm of the negated logarithm of the probability of event non-occurrence.

$$clog - \log = \log(-\log(1 - probability) \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (3)$$

The advantage of using a clog-log transformation over a logit transformation is that with the former the model invokes a proportional hazards assumption like the Cox proportional hazards model and not a proportional odds assumption as is the case with the latter (Singer & Willet, 2003; Allison, 2010). The benefit of this is that the β coefficients in the discrete-event time data are estimating the same underlying parameters as those estimated by the coefficients in the Cox proportional hazards model, and hence can be directly compared. The coefficients obtained have a relative hazard interpretation just like those from the Cox proportional hazards model. Additionally, it makes the model invariant to the time interval length i.e. months, years. The clog-log transformation has been recommended for use over the logit transformation in

cases where the underlying metric for time is truly continuous but discrete intervals are observed only due to other difficulties (measurement-related or design-related).

There are two issues that may arise with the addition of time-varying predictors that deserve mention: state and rate dependence, which are types of reverse causation (Singer & Willet, 2003). State dependence occurs when the value of a time-varying predictor in a particular interval is affected by the occurrence of the event earlier on in the same interval. Similarly, if the time-varying predictors' value is affected by the individual's value of hazard in the same period then rate-dependence is said to have occurred. For example, if the patient has suffered a recurrent AMI within the first 10 days of the quarter, his/her adherence over the latter part of the observation period may be affected by this. The suggested method to reduce ambiguity would be to lag the values of the covariates by one observation period (i.e. a quarter) (Singer & Willet, 2003; Allison, 2010). This would require the deletion of cases that had the event occurrence during the first quarter. However, since such cases are not included in the study population (based on the exclusion criteria); the lagged values of the time-varying predictors were used.

MSMs (model 3). Lastly, as mentioned above, model 3 was a MSM that aims to estimate the effects of long-term adherence to each of the 3 classes of drugs on each of the 2 outcomes under consideration, by accounting for the effects of time-dependent confounders.

It is important to understand the concept of counterfactuals (Rothman & Greenland, 1998; Hernan, Brumback, & Robins, 2002) to appreciate the utility of MSMs. Let *A(t)* be a dichotomous variable that represents exposure at time *t.* Therefore, at the end of each observation period (quarter, in our case) it can either be 0 or 1. If the study consists of *K*

observation periods, then there will be 2^K different possible values for $\bar{A}(K)$, where $\bar{A}$ represents exposure history. Let $Y_{\bar{A}}$ represent the observed outcome for a subject with exposure history $\bar{A}$. Only one value of the outcome can be observed for each subject as they have a unique exposure history. All the other outcomes are called counterfactuals. Therefore for a subject an exposure is said to have a causal effect on outcome if $Y_{\bar{A}}(t) \neq Y_{\bar{A}'}(t)$ for exposure history $\bar{A}$ and $\bar{A}'$. On a population level, there is a causal relationship if the mean outcome for a particular exposure history is not equivalent to the mean outcome for a different exposure history. Therefore for each $\bar{A}$, a MSM model can be specified as,

$$\lambda_{Y_{\bar{A}}}(t|X) = \lambda_0(t)\exp[\beta_1 a(t) + \beta_2 X] \quad \text{.....(4)}$$

where $\lambda_{Y_{\bar{A}}}(t|X)$ is the hazard of death at time t among subjects with baseline covariates X, had they all followed treatment history $\bar{A}$. β_1 and β_2 are the parameters to be estimated and λ_0 is the baseline hazard function.

The model is fitted in a two-stage process. First, the probability of each subject having his/her own treatment history is estimated which is then used to derive inverse-probability-of-treatment weights (IPTWs). Second, these weights are then used while estimating the adherence-outcome association via a regression model.

The IPTWs, in practice tend to be non-normally distributed and highly variable. Therefore the use of stabilized weights has been recommended (Hernan et al., 2000; 2002), due

to the smaller variance and narrower 95% CI intervals obtained[2]. These are derived using the following equation,

$$SW(t) = \prod_{k=0}^{t} \frac{f[A(k)|\bar{A}(k-1),V]}{f[A(k)|\bar{A}(k-1),\bar{L}(k)]} \quad \text{.....(5)}$$

where *A(k)* represents the treatment at time *k* and $\bar{A}(k-1)$ represents the prior treatment history, *V* represents the baseline covariates, and $\bar{L}(k)$ represents the time-varying covariates through time *k* inclusive of the baseline covariates. Essentially, the numerator can be thought of as the conditional probability of a subject receiving his/her own observed treatment at time *k*, given the prior treatment history and baseline covariates. Similarly, the denominator represents the conditional probability of a subject receiving his/her own observed treatment at time *k*, given the prior treatment history and prognostic factors (it accounts for the predictive effect of the time-varying covariates). To estimate the IPTW, separate logistic regression models were used for the numerator and the denominator (see Faries & Kadziola, 2012 for SAS codes; see Fewell et al. 2004 for STATA commands), with adherence being the dependent variable in both. Estimation of the numerator included the baseline covariates as independent variables, whereas estimation of the denominator included time-varying covariates too.

To account for subject drop-out before the end of the study period, the inverse-probability of-censoring weight was estimated in a similar fashion as the IPTW above. The stabilized version of this weight is,

$$SW'(t) = \prod_{k=0}^{t} \frac{P[C(k)=0|\bar{C}(k-1)=0,\bar{A}(k-1),V,T>k]}{P[C(k)=0|\bar{C}(k-1)=0,\bar{A}(k-1),\bar{L}(k-1),T>k]} \quad \text{.....(6)}$$

[2] MSMs using normalized stabilized weights (Xiao, Abrahamowicz, & Moodie, 2010) were also fitted to the data as the variability of the stabilized weights was not found to be optimum. The results of MSMs using normalized stabilized weights are reported in Appendix C – Additional Results.

where *C(t)* represents if the subject is censored, taking the value 1 when censored at time *t* and 0 when not and $\bar{C}(t)$ denotes the censoring history. Therefore, the numerator can be thought of as the conditional probability of the subject not being censored at time *k*, given his prior censoring and treatment history inclusive of baseline covariates. The denominator is essentially the same, other than the fact that it incorporates the time-varying predictors. The estimation of the censoring weights was carried out in a similar fashion as that of the treatment weights. Logistic regression was used to estimate the numerator and the denominator (see Faries & Kadziola, 2012 for SAS codes; see Fewell et al. 2004 for STATA commands). A binary flag indicating whether the subject was censored was used as the dependent variable.

On accounting for censoring, the equation for the estimation of the stabilized IPTWs changes to

$$SW(t) = \prod_{k=0}^{t} \frac{f[A(k)|\bar{A}(k-1),V,C(k)=0]}{f[A(k)|\bar{A}(k-1),\bar{L}(k),C(k)=0]} \quad \text{.....(7)}$$

However, this does not make any difference while computing the weights.

The final weight for each subject's observation is a product of the IPTWs and censoring weights, given as

$$SW(t) \times SW'(t) \quad \text{.....(8)}$$

To implement the final MSM a Cox proportional hazard model was used with each person-quarter as an observation for weighting. Lagged observations were used. Additionally, weighing introduces within subject correlation, therefore, robust sandwich variance estimators were derived (see Faries & Kadziola, 2012 for SAS codes; see Fewell et al. 2004 for STATA commands).

The MSMs provide consistent estimates of the causal inference based on three assumptions: 1) no unmeasured confounders, 2) there exists a positive probability for each treatment for each set of covariates and 3) specification of the correct models to estimate the weights and carry out the analysis. Several methods to study the sensitivity of the MSM to the presence of unmeasured confounding have been suggested (Robins, 1999; Brumback, Hernan, Haneuse, & Robins, 2004). One of the methods suggested is to measure the amount of such confounding through a sensitivity parameter, called alpha and confounding function. It stands for a measure of how different the potential outcomes are for patients in different treatment groups. Faries & Kadziola, 2012 provide a detailed method for computation of alpha using SAS. Similarly, the positivity assumption can be assessed by estimating the probability of being adherent using all possible covariates across all observation periods (Mortimer, Neugebauer, van der Laan & Tager, 2005). However, this is beyond the scope of this study and will be followed up in subsequent research.

Aim 4: To compare predictive values of adherence measured as a time-varying and time-invariant variable in assessing the risk of subsequent outcomes.

Four models have been specified so far, a Cox proportional hazard model with adherence as time-invariant predictor, two discrete-event time models, one with and one without time-varying predictors and lastly a MSM (not including the continuous time models). The estimates of the association between long-term adherence and outcomes obtained from each of these was compared against each other and to the estimates obtained from previous randomized controlled trials and observational studies.

Model that are nested (discrete-event time models 1 & 2) can be compared using the deviance statistic (-2 log likelihood $_{\text{current model}}$). When a series of models are fit to the same data, the smaller the deviance statistic, the better the fit of the model (Singer & Willett, 2003).

The relative-goodness of fit of models that are not nested within each other can be compared using the Akaike Information Criterion (AIC) and the Bayesian Information Criterion (BIC) as long as they are fit to the same data (Singer & Willett, 2003). The model with the smaller AIC and/or BIC is the one with the better fit. The general consensus for the BIC is that a difference of 0 to 2 points suggests a weak improvement, 2 to 6 – positive, 6 to 10 – strong, and > 10 very strong. However, it should be kept in mind that these are just guidelines and it is not an exact science. The various goodness-of-fit statistics for all the models have been reported.

CHAPTER 4

RESULTS

Baseline Sample Characteristics

As discussed in the methods section, a total of 1,427 patients were included in the study after applying the inclusion and exclusion criteria. Of the 1,427 patients, cohort A (statin therapy) comprised of 1,091 patients, and cohorts B (β-blocker therapy) and C (ACEI/ARB therapy) included 1,021 and 1,025 patients, respectively, based on their prescription records. Table II presents the socio-demographic and other baseline characteristics of all 1,427 subjects, as well as the distribution of the characteristics across all three study cohorts. The 1,427 patients were approximately equally distributed across the age groups: 65-70 years (20.32%), 71-75 years (22.56%), 76-80 years (21.65%), 81-85 years (16.75%), and >85 years (18.71%). A majority of the patients were female (61.53%), White (84.72%), and resided in the Southern region of the U.S. (44.50%). The average CCI score of the sample was 6.67 (±3.41). For a majority of the patients the length of hospital stay associated with the initial episode of AMI was less than 7 days (68.40%) and a minority had either a CABG (11.42%) or a PCI (36.23%) procedure performed during that stay. As far as prior history is concerned, 11.49% of the total sample had been diagnosed with Angina and 45.20% had prior CAD. Almost half of the patients were already on statin (44.36%), β-blocker (47.37%) or ACEI/ARB therapy (52.07%) before the initial AMI episode. The socio-demographic and baseline characteristic distribution across cohorts A, B, and C was similar to that of the total sample (Table II).

Table II Baseline sample characteristics

	All Subjects N (1,427)		Cohort A (Statin Therapy) N (1,091)		Cohort B (β-blocker therapy) N (1,021)		Cohort C (ACEI/ARB Therapy) N (1,025)	
Age, *n (%)*								
65 - 70 years	290	20.32	237	21.72	221	21.65	207	20.20
71 - 75 years	322	22.56	263	24.11	232	22.72	251	24.49
76 - 80 years	309	21.65	223	20.44	225	22.04	213	20.78
81 - 85 years	239	16.75	187	17.14	162	15.87	170	16.59
> 85 years	267	18.71	181	16.59	181	17.73	184	17.95
Gender, *n (%)*								
Male	549	38.47	433	39.69	396	38.79	378	36.88
Female	878	61.53	658	60.31	625	61.21	647	63.12
Ethnicity, *n (%)*								
White	1,209	84.72	924	84.69	875	85.7	869	84.78
Black	124	8.69	92	8.43	85	8.33	87	8.49
Other	94	6.59	75	6.87	61	5.97	69	6.73
Region of US, *n (%)*								
Northeast	218	15.28	176	16.13	154	15.08	162	15.80
Midwest	385	26.98	299	27.41	284	27.82	272	26.54
South	635	44.50	456	41.80	446	43.68	454	44.29
West	189	13.24	160	14.67	137	13.42	137	13.37
CCI, *mean (SD)*	6.67	3.41	6.62	3.44	6.36	3.26	6.68	3.44
Length of Hospital Stay, *n (%)*								
< 7 days	976	68.40	748	68.56	705	69.05	714	69.66
≥ 7 days	451	31.60	343	31.44	316	30.95	311	30.34
Surgical Procedure, *n (%)*								
CABG	163	11.42	140	12.83	131	12.83	99	9.66
PCI	517	36.23	425	38.96	401	39.28	402	39.22
Prior Angina, *n (%)*	164	11.49	123	11.27	94	9.21	110	10.73
Prior CAD, *n (%)*	645	45.20	488	44.73	405	39.67	460	44.88
Prior Therapy, *n (%)*								
Prior Statin Therapy	633	44.36	553	50.69	427	41.82	453	44.20
Prior β-blocker Therapy	676	47.37	512	46.93	480	47.01	497	48.49
Prior ACEI/ARB Therapy	743	52.07	548	50.23	507	49.66	619	60.39
Concurrent Therapy, *n (%)*								
Concurrent Statin Therapy	1,091	76.45	—	—	770	75.42	775	75.61
Concurrent β-blocker Therapy	1,021	71.55	770	70.58	—	—	724	70.63
Concurrent ACEI/ARB Therapy	1,025	71.83	775	71.04	724	70.91	—	—

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

Aim 1: Predictors of Time-invariant Adherence

Based on the time-invariant 1 year adherence measure, 60.71% of the patients in cohort A were adherent to statin therapy, when a measure of ≥0.8 was defined as adherent (see Chapter 3, Methods for a detail description of how adherence was computed). Similarly, 61.39% of the patients in cohort B and 56.05% of the patients in cohort C were adherent to β-blocker and ACEI/ARB therapy, respectively. Table III presents predictors of the time-invariant 1 year adherence measure in cohorts A, B, and C, respectively.

Age emerged as a significant predictor of adherence to current β-blocker therapy. The odds of being adherent were higher for patients in the 76-80 year old (Odds Ratio (OR) = 1.75; 95% CI [1.14, 2.69]; $p < 0.0104$) and 81-85 year old (OR = 1.86; 95% CI [1.67, 2.97]; $p = 0.0092$) age groups, when compared to >85 year old patients. Males (OR = 0.68; 95% CI [0.51, 0.90]; $p < 0.0072$) were also less likely to be adherent to their β-blocker therapy when compared to females. White patients had significantly higher odds of being adherent to statin therapy (OR = 1.62; 95% CI [1.02, 2.56]; $p = 0.0407$), when compared to Black patients. Among cohort B patients, those residing in the Northeast had higher odds of being adherent, when compared to their counterparts in the South (OR = 1.70; 95% CI [1.17, 2.59]; $p < 0.0134$).

Prior therapy also emerged as a significant predictor of adherence across all three cohorts. Patients on prior statin therapy were more likely to adhere to their current statin therapy when compared to patients not on prior statin therapy (OR = 1.89; 95% CI [1.41, 2.53]; $p < .0001$). Similarly, patients on prior ACEI/ARB therapy were more likely to adhere to their current statin therapy when compared to patients not on prior ACEI/ARB therapy (OR = 1.37; 95% CI [1.02, 1.83]; $p < 0.0356$). Patients on prior β-blocker therapy were more likely to adhere to

Table III Predictors of time-invariant adherence

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Age									
65 - 70 years	0.79	[0.50, 1.23]	0.2960	1.41	[0.92, 2.18]	0.1184	0.94	[0.59, 1.49]	0.7933
71 - 75 years	0.82	[0.53, 1.27]	0.3732	1.39	[0.90, 2.14]	0.1335	1.43	[0.92, 2.24]	0.1168
76 - 80 years	0.76	[0.49, 1.19]	0.2366	1.75	[1.14, 2.69]	0.0104*	1.10	[0.70, 1.73]	0.6737
81 - 85 years	0.69	[0.44, 1.09]	0.1082	1.86	[1.67, 2.97]	0.0092*	1.10	[0.69, 1.76]	0.6945
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.10	[0.83, 1.45]	0.5078	0.68	[0.51, 0.90]	0.0072*	0.91	[0.68, 1.22]	0.5140
Female	Ref			Ref			Ref		
Ethnicity									
White	1.62	[1.02, 2.56]	0.0407*	1.56	[0.97, 2.51]	0.0663	1.01	[0.60, 1.70]	0.9767
Other	1.44	[0.73, 2.82	0.2903	1.08	[0.53, 2.17]	0.8386	0.81	[0.39, 1.68]	0.5658
Black	Ref			Ref			Ref		
Region of US									
Northeast	1.28	[0.86, 1.89]	0.2197	1.70	[1.17, 2.59]	0.0134*	1.12	[0.74, 1.70]	0.5834
Midwest	1.27	[0.92, 1.76]	0.1500	1.37	[0.99, 1.91]	0.0567	1.18	[0.84, 1.67]	0.3380
West	0.98	[0.65, 1.47]	0.9195	0.92	[0.61, 1.38]	0.6719	0.91	[0.59, 1.41]	0.6743
South	Ref								
CCI	0.99	[0.95, 1.03]	0.6515	1.01	[0.96, 1.05]	0.7320	0.96	[0.92, 1.00]	0.0694
Length of Hospital Stay									
< 7 days	1.05	[0.76, 1.50]	0.7527	1.00	[0.72, 1.38]	0.9837	0.91	[0.65, 1.27]	0.5824
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	1.56	[0.96, 2.54]	0.0712	1.31	[0.81, 2.12]	0.2653	1.03	[0.61, 1.76]	0.9034
PCI	1.31	[0.97, 1.78]	0.0822	1.18	[0.87, 1.61]	0.2847	1.27	[0.92, 1.74]	0.1422

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	OR	95% CI	*p*	OR	95% CI	*p*	OR	95% CI	*p*
Prior Angina	0.94	[0.61, 1.44]	0.7697	1.49	[0.89, 2.50]	0.1313	1.13	[0.70, 1.81]	0.6234
Prior CAD	0.78	[0.58, 1.06]	0.1117	0.83	[0.61, 1.13]	0.2345	0.81	[0.59, 1.11]	0.1914
Prior Therapy									
Prior Statin Therapy,	1.89	[1.41, 2.53]	<.0001*	1.15	[0.86, 1.55]	0.3524	1.20	[0.88, 1.63]	0.2408
Prior β-blocker Therapy	0.96	[0.72, 1.28]	0.7930	1.54	[1.14, 2.08]	0.0054*	1.01	[0.75, 1.38]	0.9363
Prior ACEI/ARB Therapy	1.37	[1.02, 1.83]	0.0356*	0.75	[0.56, 1.00]	0.0512	3.68	[2.72, 4.97]	<.0001*
Concurrent Therapy									
Concurrent Statin Therapy	—	—	—	0.87	[0.63, 1.21]	0.4028	1.26	[0.91, 1.76]	0.1704
Concurrent β-blocker Therapy	1.07	[0.80, 1.44]	0.6556	—	—	—	1.09	[0.80, 1.48]	0.6042
Concurrent ACEI/ARB Therapy	1.13	[0.83, 1.52]	0.4377	1.13	[0.84, 1.53]	0.4286	—	—	—

*$p<0.05$

OR, Odds Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

their current β-blocker therapy, when compared to patients not on prior therapy (OR = 1.54; 95% CI [1.14, 2.08]; $p < 0.0054$) and the odds of being adherent to current ACEI/ARB therapy were significantly higher for patients on prior ACEI/ARB therapy when compared to patients not on prior ACEI/ARB therapy (OR = 3.68; 95% CI [2.72, 4.97]; $p < .0001$).

Aim 2: Time-invariant Adherence as a Predictor of Outcomes

Model 1: Baseline covariates and time-invariant adherence as predictors.

Recurrent AMI. Table IV presents the results of the Cox proportional hazards model estimating the effect of time-invariant adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of a recurrent AMI. Time-invariant adherence to statins was not significantly associated with the hazard of a recurrent AMI (Hazard Ratio (HR) = 0.73; 95% CI [0.47, 1.15]; $p = 0.1707$); neither was adherence to β-blockers (HR = 0.95; 95% CI [0.59, 1.54]; $p = 0.8435$), nor ACEI/ARBs (HR = 0.98; 95% CI [0.61, 1.58]; $p = 0.9381$).

The hazard of a recurrent AMI increased significantly with age. This was observed across all three study cohorts. Patients aged between 65-70 years (Hazard Ratio (HR) = 0.45; 95% CI [0.23, 0.90]; $p = 0.0246$) and 76-80 years (HR = 0.49; 95% CI [0.25, 0.97]; $p = 0.0419$) in cohort A had a significantly lower hazard of a recurrent AMI when compared to patients >85 year old. Similarly, in cohorts B and C, 71-75 year olds (cohort B: HR = 0.46; 95% CI [0.22, 0.96]; $p = 0.0380$, cohort C: HR = 0.47; 95% CI [0.24, 0.90]; $p = 0.0227$) and 76-80 year olds (cohort B: HR = 0.47; 95% CI [0.23, 0.97]; $p = 0.0406$, cohort C: HR = 0.43; 95% CI [0.21, 0.86]; $p = 0.0177$) had a lower hazard of recurrent AMI, when compared to elderly patients >85 year old. Among Cohort A patients, those residing in the Western region of the country had a

Table IV Model 1: Predictors of the hazard of a recurrent AMI

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.45	[0.23, 0.90]	0.0246*	0.55	[0.27, 1.12]	0.0982	0.55	[0.28, 1.09]	0.0849
71 - 75 years	0.53	[0.28, 1.00]	0.0513	0.46	[0.22, 0.96]	0.0380*	0.47	[0.24, 0.90]	0.0227*
76 - 80 years	0.49	[0.25, 0.97]	0.0419*	0.47	[0.23, 0.97]	0.0406*	0.43	[0.21, 0.86]	0.0177*
81 - 85 years	0.62	[0.32, 1.19]	0.1515	1.02	[0.54, 1.95]	0.9435	0.86	[0.46, 1.61]	0.6281
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.07	[0.67, 1.68]	0.7885	1.10	[0.68, 1.79]	0.7016	1.14	[0.72, 1.80]	0.5846
Female	Ref			Ref			Ref		
Ethnicity									
White	1.28	[0.60, 2.71]	0.5191	1.81	[0.71, 4.62]	0.2111	0.84	[0.43, 1.66]	0.6178
Other	1.05	[0.33, 3.31]	0.9388	1.95	[0.54, 6.96]	0.3063	0.52	[0.16, 1.70]	0.2761
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.82	[0.46, 1.46]	0.4962	0.86	[0.45, 1.63]	0.6362	0.60	[0.32, 1.14]	0.1173
Midwest	0.65	[0.38, 1.13]	0.1286	0.75	[0.43, 1.32]	0.3219	0.67	[0.39, 1.15]	0.1450
West	0.38	[0.17, 0.87]	0.0216*	0.59	[0.27, 1.29]	0.1883	0.72	[0.37, 1.43]	0.3462
South	Ref			Ref			Ref		
CCI	1.09	[1.03, 1.16]	0.0050*	1.15	[1.08, 1.23]	<.0001*	1.12	[1.06, 1.19]	0.0002*
Length of Hospital Stay									
< 7 days	1.12	[0.67, 1.85]	0.6717	1.86	[1.03, 3.36]	0.0408*	1.33	[0.79, 2.24]	0.2768
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.40	[0.15, 1.08]	0.0703	0.66	[0.24, 1.81]	0.4204	0.65	[0.24, 1.73]	0.3857

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.47	[0.27, 0.80]	0.0055*	0.55	[0.32, 0.94]	0.0275*	0.65	[0.40, 1.08]	0.0962
Prior Angina	1.48	[0.83, 2.66]	0.1865	1.09	[0.54, 2.18]	0.8188	1.49	[0.84, 2.67]	0.175
Prior CAD	1.10	[0.67, 1.82]	0.7016	0.97	[0.57, 1.60]	0.8645	1.18	[0.71, 1.94]	0.5274
Prior Therapy									
Prior Statin Therapy,	0.86	[0.54, 1.37]	0.5224	1.12	[0.68, 1.85]	0.6492	1.17	[0.73, 1.88]	0.5096
Prior β-blocker Therapy	1.39	[0.87, 2.22]	0.1737	1.43	[0.86, 2.38]	0.1684	1.50	[0.93, 2.42]	0.0958
Prior ACEI/ARB Therapy	0.99	[0.61, 1.60]	0.9689	1.19	[0.72, 1.95]	0.4954	0.88	[0.53, 1.45]	0.6099
Concurrent therapy									
Concurrent Statin Therapy	–	–	–	0.82	[0.48, 1.41]	0.4715	0.94	[0.56, 1.59]	0.8203
Concurrent β-blocker Therapy	0.98	[0.62, 1.57]	0.9449	–	–	–	1.13	[0.70, 1.81]	0.6257
Concurrent ACEI/ARB Therapy	1.44	[0.85, 2.44]	0.1716	1.32	[0.77, 2.28]	0.3169	–	–	–
TIME-CONSTANT ADHERENCE									
Statin Adherence	0.73	[0.47, 1.15]	0.1707	–	–	–	–	–	–
β-blocker Adherence	–	–	–	0.95	[0.59, 1.54]	0.8435	–	–	–
ACEI/ARB Adherence	–	–	–	–	–	–	0.98	[0.61, 1.58]	0.9381

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

significantly lower hazard of a recurrent AMI when compared to patients from the South (HR = 0.38; 95% CI [0.17, 0.87]; $p = 0.0216$).

As far as clinical characteristics are concerned, the hazard of a recurrent AMI increased significantly with a patient's CCI across all three cohorts (cohort A: HR = 1.09; 95% CI [1.03, 1.16]; $p = 0.0050$, cohort B: HR = 1.15; 95% CI [1.08, 1.23]; $p < .0001$, cohort C: HR = 1.12; 95% CI [1.06, 1.19]; $p = 0.0002$). Among cohort B patients, those that were hospitalized for less than a week for their initial AMI had a higher hazard of a recurrent episode when compared to patients with a hospital stay ≥7 days (HR = 1.86; 95% CI [1.03, 3.36]; $p = 0.0408$). Finally, a significantly lower hazard of a recurrent AMI was observed among patients that had a PCI procedure performed during their initial hospital stay when compared to patients that did not have the surgery performed (cohort A: HR = 0.47; 95% CI [0.27, 0.80]; $p = 0.0055$, cohort B: HR = 0.55; 95% CI [0.32, 0.94]; $p = 0.0275$).

Mortality. Table V presents the results of the Cox proportional hazards model estimating the effect of time-invariant adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of mortality. Time-invariant adherence to statins was not significantly associated with the hazard of mortality (HR = 0.73; 95% CI [0.53, 1.00]; $p = 0.0531$); neither was adherence to β-blockers (HR = 1.21; 95% CI [0.86, 1.71]; $p = 0.2704$), nor ACEI/ARBs (HR = 1.04; 95% CI [0.75, 1.44]; $p = 0.8215$).

The hazard of death increased significantly with age across all three cohorts. Patients aged between 65-70 years (cohort A: HR = 0.39; 95% CI [0.23, 0.65]; $p = 0.0003$, cohort B: HR = 0.23; 95% CI [0.13, 0.40]; $p < .0001$, cohort C: HR = 0.38; 95% CI [0.23, 0.62]; $p = 0.0002$), 71-75 years (cohort A: HR = 0.41; 95% CI [0.26, 0.67]; $p = 0.0003$, cohort B: HR = 0.27; 95%

CI [0.16, 0.46]; $p < .0001$, cohort C: HR = 0.35; 95% CI [0.22, 0.56]; $p < .0001$), 76-80 years (cohort A: HR = 0.47; 95% CI [0.29, 0.76]; $p = 0.0021$, cohort B: HR = 0.27; 95% CI [0.17, 0.44]; $p < .0001$, cohort C: HR = 0.42; 95% CI [0.27, 0.64]; $p < .0001$), and 81-85 years (cohort A: HR = 0.64; 95% CI [0.41, 0.99]; $p = 0.0475$, cohort B: HR = 0.59; 95% CI [0.38, 0.90]; $p = 0.0153$) had a lower hazard of death, when compared to elderly patients >85 years old.

Among clinical characteristics, the hazard of death increased significantly with a patient's CCI across all three cohorts (cohort A: HR = 1.14; 95% CI [1.09, 1.19]; $p < .0001$, cohort B: HR = 1.16; 95% CI [1.10, 1.21]; $p < .0001$, cohort C: HR = 1.13; 95% CI [1.08, 1.18]; $p < .0001$). Patients that had a CABG surgery performed during their initial hospital stay had a significantly lower hazard of death (cohort A: HR = 0.25; 95% CI [0.11, 0.55]; $p = 0.0006$, cohort B: HR = 0.39; 95% CI [0.18, 0.84]; $p = 0.0154$, cohort C: HR = 0.28; 95% CI [0.12, 0.64]; $p = 0.0029$), when compared to patients that did not have the surgery. Similar results were obtained for a PCI procedure (cohort A: HR = 0.29; 95% CI [0.18, 0.46]; $p < .0001$, cohort B: HR = 0.31; 95% CI [0.19, 0.49]; $p < .0001$, cohort C: HR = 0.33; 95% CI [0.22, 0.51]; $p < .0001$), whereby patients that had the procedure performed were less likely to die than those that did have the procedure performed.

Patients that were on ACEI/ARB therapy prior to the initial AMI episode had a significantly higher hazard of death (HR = 1.74; 95% CI [1.20, 2.52]; $p = 0.0035$), when compared to patients with no prior history of ACEI/ARB therapy among cohort C patients. Additionally, among cohort B and C patients, those that were on concomitant statin therapy reported a significantly lower hazard of death, in comparison to patients that were not on concomitant statin therapy (cohort B: HR = 0.61; 95% CI [0.43, 0.86]; $p = 0.0056$, cohort C: HR = 0.63; 95% CI [0.46, 0.88]; $p = 0.0058$).

Table V Model 1: Predictors of the hazard of death

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.39	[0.23, 0.65]	0.0003*	0.23	[0.13, 0.40]	<.0001*	0.38	[0.23, 0.62]	0.0002*
71 - 75 years	0.41	[0.26, 0.67]	0.0003*	0.27	[0.16, 0.46]	<.0001*	0.35	[0.22, 0.56]	<.0001*
76 - 80 years	0.47	[0.29, 0.76]	0.0021*	0.27	[0.17, 0.44]	<.0001*	0.42	[0.27, 0.64]	<.0001*
81 - 85 years	0.64	[0.41, 0.99]	0.0475*	0.59	[0.38, 0.90]	0.0153*	0.72	[0.48, 1.08]	0.1145
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.25	[0.90, 1.74]	0.1803	1.41	[1.00, 1.99]	0.0491	1.15	[0.84, 1.59]	0.3822
Female	Ref			Ref			Ref		
Ethnicity									
White	0.95	[0.59, 1.55]	0.8484	1.09	[0.63, 1.88]	0.7639	0.81	[0.52, 1.28]	0.3685
Other	1.00	[0.49, 2.04]	0.9898	0.90	[0.40, 2.06]	0.8063	0.60	[0.29, 1.23]	0.1596
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.76	[0.49, 1.18]	0.2232	0.76	[0.48, 1.20]	0.2362	0.66	[0.43, 1.01]	0.0561
Midwest	0.95	[0.64, 1.41]	0.8124	0.72	[0.48, 1.07]	0.1067	0.75	[0.51, 1.09]	0.1320
West	0.67	[0.40, 1.12]	0.1248	0.59	[0.33, 1.04]	0.0665	0.79	[0.49, 1.27]	0.3303
South	Ref			Ref			Ref		
CCI	1.14	[1.09, 1.19]	<.0001*	1.16	[1.10, 1.21]	<.0001*	1.13	[1.08, 1.18]	<.0001*
Length of Hospital Stay									
< 7 days	0.93	[0.66, 1.31]	0.6650	0.99	[0.69, 1.41]	0.9368	0.81	[0.59, 1.10]	0.1739
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.25	[0.11, 0.55]	0.0006*	0.39	[0.18, 0.84]	0.0154*	0.28	[0.12, 0.64]	0.0029*

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.29	[0.18, 0.46]	<.0001*	0.31	[0.19, 0.49]	<.0001*	0.33	[0.22, 0.51]	<.0001*
Prior Angina	1.04	[0.66, 1.66]	0.8593	0.63	[0.36, 1.11]	0.1128	1.07	[0.68, 1.69]	0.7618
Prior CAD	0.98	[0.68, 1.40]	0.9116	1.21	[0.85, 1.73]	0.2848	1.11	[0.80, 1.55]	0.5233
Prior Therapy									
Prior Statin Therapy,	0.97	[0.69, 1.37]	0.8718	1.13	[0.79, 1.62]	0.5015	0.91	[0.66, 1.26]	0.5775
Prior β-blocker Therapy	0.81	[0.59, 1.13]	0.2248	1.08	[0.77, 1.53]	0.6638	0.77	[0.56, 1.04]	0.0890
Prior ACEI/ARB Therapy	1.34	[0.94, 1.91]	0.1043	1.24	[0.88, 1.77]	0.2241	1.74	[1.20, 2.52]	0.0035*
Concurrent therapy									
Concurrent Statin Therapy	–	–	–	0.61	[0.43, 0.86]	0.0056*	0.63	[0.46, 0.88]	0.0058*
Concurrent β-blocker Therapy	0.91	[0.65, 1.26]	0.5675	–	–	–	0.91	[0.67, 1.24]	0.5621
Concurrent ACEI/ARB Therapy	1.13	[0.79, 1.63]	0.5107	1.13	[0.78, 1.62]	0.5204	–	–	–
TIME-CONSTANT ADHERENCE									
Statin Adherence	0.73	[0.53, 1.00]	0.0531	–	–	–	–	–	–
β-blocker Adherence	–	–	–	1.21	[0.86, 1.71]	0.2704	–	–	–
ACEI/ARB Adherence	–	–	–	–	–	–	1.04	[0.75, 1.44]	0.8215

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

Time-varying Confounders

The total study cohort comprising of 1,427 subjects were followed for an average 7.64 and median 8 quarters (Table VI). They contributed to a total of 10,904 person-quarter observations. Patients in cohorts A, B, and C contributed to a total of 8,497, 7,920, and 7,832 person-quarters, respectively. Table VII (a and b) presents the descriptives of the time-varying confounders over the observed time-period for all study subjects. (Refer to Appendix C – Additional Results, Tables XX, XXI, and XXII for descriptive statistics of time-varying confounders over the observed quarters for cohorts A, B, and C, respectively.)

Table VI Quarters observed

	Quarters Observed							
	N	Mean	SD	Median	Mode	Min	Max	Range
All Subjects	1,427	7.64	2.01	8	8	1	11	10
Cohort A (Statin Therapy)	1,091	7.79	1.87	8	8	2	11	9
Cohort B (β-blocker Therapy)	1,021	7.76	1.94	8	8	1	11	10
Cohort C (ACEI/ARB Therapy)	1,025	7.64	2.02	8	8	2	11	9

SD, standard deviation; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Table VIIa Time-varying confounders for all subjects

	Quarters Observed											
	1		2		3		4		5		6	
	N = 1,427		N = 1,426		N = 1,371		N = 1,322		N = 1,282		N = 1,241	
No. of office/outpatient visits, *mean (SD)*	16.57	13.90	11.87	12.01	10.32	10.50	9.74	10.63	9.85	11.49	9.24	9.99
Hospitalization visit (any cause), *n (%)*	199	13.95	119	8.35	92	6.71	61	4.61	70	5.46	56	4.51
Emergency room visit (any cause), *n (%)*	244	17.10	172	12.06	131	9.56	121	9.15	115	8.97	102	8.22
Receipt of PCI and/or CABG, n (%)	64	4.48	20	1.40	13	0.95	7	0.53	14	1.09	14	1.13
Presence of claim related to risk factors, *n (%)*	1,252	87.74	1,105	77.49	1,017	74.18	956	72.31	910	70.98	897	72.28
Presence of claim related to low-survival rate conditions, *n (%)*	254	17.80	230	16.13	203	14.81	170	12.86	182	14.20	179	14.42
No. of unique prescription claims, *mean (SD)*	9.91	4.07	8.15	4.01	7.82	4.01	7.88	4.06	7.69	3.95	7.59	3.9
Part D coverage gap, *n (%)*	427	29.92	507	35.55	590	43.03	527	39.86	447	34.87	403	32.47
Out of pocket Medicare costs, *mean (SD)*	520.63	653.46	534.13	666.47	517.22	828.59	475.26	577.83	471.13	1011.24	439.22	598.76

	Quarters Observed											
	1		2		3		4		5		6	
	N = 1,427		N = 1,426		N = 1,371		N = 1,322		N = 1,282		N = 1,241	
Recurrent AMI, *n (%)*	—	—	30	2.10	18	1.31	20	1.51	24	1.87	15	1.21

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Table VIIb Time-varying confounders for all subjects

	Quarters Observed									
	7		8		9		10		11	
	N = 1,217		N = 871		N = 507		N = 229		N = 11	
Number of office/outpatient visits, *mean (SD)*	8.6	10.25	7.75	12.96	7.19	10.97	4.79	6.93	0.27	0.47
Hospitalization visit (any cause), *n (%)*	58	4.77	42	4.82	12	2.37	5	2.18	0	0.00
Emergency room visit (any cause), *n (%)*	97	7.97	54	6.20	25	4.93	10	4.37	0	0.00
Receipt of PCI and/or CABG, n (%)	12	0.99	7	0.80	1	0.20	2	0.87	0	0.00
Presence of claim related to risk factors, *n (%)*	773	63.52	517	59.36	280	55.23	105	45.85	1	9.09
Presence of claim related to low-survival rate conditions, *n (%)*	164	13.48	115	13.20	55	10.85	15	6.55	0	0.00
Number of unique prescription claims, *mean (SD)*	7.04	4.17	6.63	4.17	6.44	3.99	5.47	4.25	1.36	1.69
Part D coverage gap, *n (%)*	401	32.95	339	38.92	226	44.58	100	43.67	6	54.55
Out of pocket Medicare costs, *mean (SD)*	383.34	553.49	329.28	554.35	310.76	479.68	197.19	369.42	18.83	31.24
Recurrent AMI, *n (%)*	16	1.31	10	1.15	3	0.59	2	0.87	0	0.00

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Aim 3: Time-varying Adherence as a Predictor of Outcomes

Model 2: Baseline covariates and time-varying adherence as predictors.

Recurrent AMI. Table VIII presents the results of a discrete-event time model estimating the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of a recurrent AMI. Time-varying statin adherence was associated with a lower hazard of a recurrent AMI (HR = 0.63; 95% CI [0.40, 0.99]; $p = 0.0471$) among cohort A patients. Time-varying adherence to β-blockers was not significantly associated with the hazard of a recurrent AMI (HR = 1.12; 95% CI [0.67, 1.89]; $p = 0.6622$); neither was adherence to ACEI/ARBs (HR = 1.57; 95% CI [0.93, 2.67]; $p = 0.0931$).

The hazard of a recurrent AMI increased significantly with age. Patients aged between 65-70 years (cohort A: HR = 0.50; 95% CI [0.25, 0.99]; $p = 0.0480$), 71-75 years (cohort C: HR = 0.48; 95% CI [0.25, 0.93]; $p = 0.0302$), 76-80 years (cohort C: HR = 0.43; 95% CI [0.21, 0.88]; $p = 0.0199$) had a lower hazard of a recurrent AMI, when compared to elderly patients >85 years old. Among patients in cohort A, those residing in the Western region of the country had a significantly lower hazard of a recurrent AMI (HR = 0.40; 95% CI [0.18, 0.90]; $p = 0.0261$], when compared to patients from the South.

The hazard of a recurrent AMI increased significantly with an increase in the CCI across all three cohorts (cohort A: HR = 1.09; 95% CI [1.02, 1.16]; $p = 0.0067$, cohort B: HR = 1.13; 95% CI [1.06, 1.21]; $p = 0.0002$, cohort C: HR = 1.12; 95% CI [1.05, 1.18]; $p = 0.0003$). Among cohort B patients, a <7 day hospitalization for the initial AMI was associated with a higher hazard of a recurrent episode, in comparison to a week or longer hospital stay (HR = 1.82; 95% CI [1.01, 3.29]; $p = 0.0472$). Additionally, patients that underwent a PCI procedure during their

Table VIII Model 2: Predictors of the hazard of a recurrent AMI

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.50	[0.25, 0.99]	0.0480*	0.60	[0.29, 1.22]	0.1578	0.59	[0.30, 1.17]	0.1293
71 - 75 years	0.56	[0.30, 1.06]	0.0734	0.49	[0.23, 1.03]	0.0596	0.48	[0.25, 0.93]	0.0302*
76 - 80 years	0.52	[0.26, 1.02]	0.0570	0.50	[0.25, 1.02]	0.0580	0.43	[0.21, 0.88]	0.0199*
81 - 85 years	0.66	[0.35, 1.26]	0.2096	1.04	[0.55, 1.98]	0.9048	0.87	[0.46, 1.62]	0.6500
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.06	[0.67, 1.68]	0.8092	1.09	[0.67, 1.78]	0.7288	1.16	[0.73, 1.83]	0.5371
Female	Ref			Ref			Ref		
Ethnicity									
White	1.25	[0.59, 2.66]	0.5575	1.77	[0.70, 4.50]	0.2294	0.85	[0.43, 1.69]	0.6480
Other	1.03	[0.33, 3.26]	0.9607	1.90	[0.53, 6.81]	0.3214	0.52	[0.16, 1.72]	0.2859
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.81	[0.46, 1.45]	0.4835	0.87	[0.46, 1.65]	0.6794	0.63	[0.33, 1.20]	0.1588
Midwest	0.65	[0.38, 1.13]	0.1285	0.75	[0.43, 1.32]	0.3236	0.67	[0.39, 1.15]	0.1481
West	0.40	[0.18, 0.90]	0.0261*	0.61	[0.28, 1.33]	0.2135	0.73	[0.37, 1.46]	0.3783
South	Ref			Ref			Ref		
CCI	1.09	[1.02, 1.16]	0.0067*	1.13	[1.06, 1.21]	0.0002*	1.12	[1.05, 1.18]	0.0003*
Length of Hospital Stay									
< 7 days	1.12	[0.68, 1.86]	0.6575	1.82	[1.01, 3.29]	0.0472*	1.35	[0.80, 2.27]	0.2598
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.42	[0.16, 1.12]	0.0840	0.69	[0.25, 1.88]	0.4625	0.67	[0.25, 1.79]	0.4189

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.48	[0.28, 0.83]	0.0078*	0.59	[0.34, 1.01]	0.0536	0.68	[0.41, 1.12]	0.1281
Prior Angina	1.50	[0.84, 2.69]	0.1724	1.16	[0.58, 2.32]	0.6660	1.50	[0.84, 2.68]	0.1679
Prior CAD	1.11	[0.68, 1.83]	0.6750	0.93	[0.56, 1.56]	0.7861	1.18	[0.72, 1.94]	0.5165
Prior Therapy									
Prior Statin Therapy,	0.85	[0.53, 1.36]	0.4948	1.12	[0.68, 1.84]	0.6547	1.20	[0.75, 1.92]	0.4556
Prior β-blocker Therapy	1.37	[0.85, 2.20]	0.1926	1.40	[0.84, 2.33]	0.1958	1.49	[0.92, 2.40]	0.1044
Prior ACEI/ARB Therapy	0.95	[0.68, 1.55]	0.8220	1.21	[0.72, 2.02]	0.4742	0.80	[0.49, 1.30]	0.3643
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.63	[0.40, 0.99]	0.0471*	0.64	[0.36, 1.12]	0.1146	0.62	[0.36, 1.05]	0.0747
Not on therapy	—	—	—	0.87	[0.46, 1.64]	0.6704	0.75	[0.41, 1.39]	0.3624
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									
Adherent	1.18	[0.64, 2.18]	0.5933	1.12	[0.67, 1.89]	0.6622	0.98	[0.55, 1.76]	0.9466
Not on therapy	1.14	[0.61, 2.16]	0.6811	—	—	—	0.89	[0.48, 1.67]	0.7199
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.27	[0.71, 2.27]	0.4294	1.19	[0.64, 2.20]	0.5821	1.57	[0.93, 2.67]	0.0931
Not on therapy	0.82	[0.43, 1.54]	0.5299	0.85	[0.44, 1.67]	0.6452	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

hospitalization associated with the initial AMI episode had a lower hazard of a recurrent AMI, when compared to patients that had no such procedure performed (HR = 0.48; 95% CI [0.28, 0.83]; $p = 0.0078$].

Mortality. The hazard ratios from a discrete-event time model estimating the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of death are presented in Table IX. Time-varying adherence to statins was not significantly associated with the hazard of mortality (HR = 0.86; 95% CI [0.61, 1.21]; $p = 0.3913$); neither was time-varying adherence to β-blockers (HR = 0.97; 95% CI [0.68, 1.38]; $p = 0.8469$), nor ACEI/ARBs (HR = 1.04; 95% CI [0.74, 1.46]; $p = 0.8189$).

The hazard of death increased significantly with age across all three cohorts. Patients aged between 65-70 years (cohort A: HR = 0.42; 95% CI [0.25, 0.70]; p = 0.0008, cohort B: HR = 0.25; 95% CI [0.14, 0.43]; p < .0001, cohort C: HR = 0.41; 95% CI [0.24, 0.67]; p = 0.0005), 71-75 years (cohort A: HR = 0.43; 95% CI [0.27, 0.70]; p = 0.0006, cohort B: HR = 0.29; 95% CI [0.17, 0.48]; p < .0001, cohort C: HR = 0.37; 95% CI [0.24, 0.59]; p < .0001), 76-80 years (cohort A: HR = 0.50; 95% CI [0.31, 0.81]; p = 0.0045, cohort B: HR = 0.30; 95% CI [0.19, 0.49]; p < .0001, cohort C: HR = 0.44; 95% CI [0.28, 0.68]; p = 0.0002), and 81-85 years (cohort B: HR = 0.63; 95% CI [0.41, 0.97]; p = 0.0359) had a lower hazard of death, when compared to elderly patients >85 years old.

Among clinical characteristics, the hazard of death increased significantly with a patient's CCI across all three cohorts (cohort A: HR = 1.14; 95% CI [1.09, 1.19]; $p < .0001$, cohort B: HR = 1.15; 95% CI [1.09, 1.20]; $p < .0001$, cohort C: HR = 1.12; 95% CI [1.08, 1.17]; $p < .0001$). Patients that had a CABG surgery performed during their initial hospital stay had a significantly

Table IX Model 2: Predictors of the hazard of death

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.42	[0.25, 0.70]	0.0008*	0.25	[0.14, 0.43]	<.0001*	0.41	[0.24, 0.67]	0.0005*
71 - 75 years	0.43	[0.27, 0.70]	0.0006*	0.29	[0.17, 0.48]	<.0001*	0.37	[0.24, 0.59]	<.0001*
76 - 80 years	0.50	[0.31, 0.81]	0.0045*	0.30	[0.19, 0.49]	<.0001*	0.44	[0.28, 0.68]	0.0002*
81 - 85 years	0.69	[0.44, 1.08]	0.1059	0.63	[0.41, 0.97]	0.0359*	0.75	[0.50, 1.13]	0.1652
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.26	[0.90, 1.75]	0.1736	1.38	[0.98, 1.95]	0.0641	1.14	[0.83, 1.58]	0.4153
Female	Ref			Ref					
Ethnicity									
White	0.94	[0.57, 1.52]	0.7868	1.08	[0.63, 1.86]	0.7796	0.84	[0.53, 1.31]	0.4347
Other	0.96	[0.47, 1.96]	0.9042	0.95	[0.42, 2.15]	0.8971	0.62	[0.30, 1.26]	0.1864
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.76	[0.49, 1.17]	0.2116	0.79	[0.50, 1.25]	0.3090	0.69	[0.45, 1.06]	0.0885
Midwest	0.95	[0.64, 1.41]	0.8100	0.77	[0.52, 1.15]	0.1965	0.76	[0.52, 1.11]	0.1598
West	0.68	[0.41, 1.14]	0.1478	0.58	[0.33, 1.03]	0.0639	0.80	[0.50, 1.28]	0.3491
South	Ref			Ref			Ref		
CCI	1.14	[1.09, 1.19]	<.0001*	1.15	[1.09, 1.20]	<.0001*	1.12	[1.08, 1.17]	<.0001*
Length of Hospital Stay									
< 7 days	0.93	[0.66, 1.32]	0.6924	0.97	[0.68, 1.39]	0.8744	0.82	[0.60, 1.13]	0.2217
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.25	[0.11, 0.56]	0.0008*	0.39	[0.18, 0.85]	0.0169*	0.28	[0.12, 0.66]	0.0034*

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.29	[0.18, 0.46]	<.0001*	0.32	[0.20, 0.50]	<.0001*	0.35	[0.23, 0.53]	<.0001*
Prior Angina	1.08	[0.69, 1.71]	0.7436	0.66	[0.38, 1.16]	0.1479	1.06	[0.67, 1.67]	0.7984
Prior CAD	1.00	[0.70, 1.43]	0.9992	1.20	[0.84, 1.71]	0.3265	1.12	[0.81, 1.57]	0.4874
Prior Therapy									
Prior Statin Therapy,	0.94	[0.67, 1.32]	0.7212	1.10	[0.77, 1.58]	0.5932	0.90	[0.65, 1.25]	0.5368
Prior β-blocker Therapy	0.81	[0.58, 1.13]	0.2157	1.10	[0.78, 1.56]	0.5940	0.76	[0.56, 1.04]	0.0865
Prior ACEI/ARB Therapy	1.28	[0.89, 1.83]	0.1770	1.23	[0.86, 1.77]	0.2592	1.74	[1.20, 2.50]	0.0032*
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.86	[0.61, 1.21]	0.3913	1.07	[0.68, 1.68]	0.7766	1.06	[0.69, 1.63]	0.7806
Not on therapy	—	—	—	1.67	[1.04, 2.67]	0.0333*	1.62	[1.04, 2.52]	0.0321*
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									
Adherent	1.02	[0.66, 1.60]	0.9206	0.97	[0.68, 1.38]	0.8469	0.91	[0.60, 1.38]	0.6524
Not on therapy	1.11	[0.71, 1.74]	0.6397	—	—	—	1.02	[0.67, 1.54]	0.9297
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.10	[0.72, 1.69]	0.6550	1.16	[0.74, 1.82]	0.5079	1.04	[0.74, 1.46]	0.8189
Not on therapy	0.96	[0.61, 1.52]	0.8727	0.97	[0.61, 1.54]	0.8930	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

lower hazard of death (cohort A: HR = 0.25; 95% CI [0.11, 0.56]; $p = 0.0008$, cohort B: HR = 0.39; 95% CI [0.18, 0.85]; $p = 0.0169$, cohort C: HR = 0.28; 95% CI [0.12, 0.66]; $p = 0.0034$), when compared to patients that did not have the surgery. Similar results were obtained for a PCI procedure (cohort A: HR = 0.29; 95% CI [0.18, 0.46]; $p < .0001$, cohort B: HR = 0.32; 95% CI [0.20, 0.50]; $p < .0001$, cohort C: HR = 0.35; 95% CI [0.23, 0.53]; $p < .0001$), whereby patients that had the procedure performed were less likely to die than those that did not have the procedure performed.

Patients that were on ACEI/ARB therapy prior to the initial AMI episode had a 74% higher hazard of death (HR = 1.74; 95% CI [1.20, 2.50]; $p = 0.0032$), when compared to patients with no prior history of ACEI/ARB therapy among cohort C patients. Additionally, among cohort B and C patients, those that were not on concomitant statin therapy reported a significantly higher hazard of death, in comparison to patients that were not adherent to concomitant statin therapy (cohort B: HR = 1.67; 95% CI [1.04, 2.67]; $p = 0.0333$, cohort C: HR = 1.62; 95% CI [1.04, 2.52]; $p = 0.0321$).

The results of continuous time models (model 2b) estimating the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of subsequent outcomes are presented in Appendix C – Additional Results, Tables XXIII and XXIV.

Model 3: Baseline covariates, time-varying confounders and time-varying adherence as predictors.

Recurrent AMI. Table X presents the results of a discrete-event time model estimating the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B,

and C, respectively, on the risk of a recurrent AMI after accounting for time-varying covariates. Cohort A patients that were adherent to their statin therapy had a significantly lower hazard of a recurrent AMI when compared to non-adherent patients (HR = 0.61; 95% CI [0.38, 0.97; p = 0.0366). Time-varying adherence to β-blockers was not significantly associated with the hazard of a recurrent AMI (HR = 1.09; 95% CI [0.65, 1.85]; p = 0.7440); neither was time-varying adherence to ACEI/ARBs (HR = 1.57; 95% CI [0.93, 2.68]; p = 0.8469).

The hazard of a recurrent AMI increased significantly with age. Patients aged between 65-70 years (cohort A: HR = 0.48; 95% CI [0.24, 0.97]; p = 0.0397), 71-75 years (cohort C: HR = 0.48; 95% CI [0.25, 0.93]; p = 0.0302), 76-80 years (cohort A: 0.50; 95% CI [0.25, 0.99]; p = 0.0470, cohort C: HR = 0.43; 95% CI [0.21, 0.88]; p = 0.0203) had a lower hazard of a recurrent AMI, when compared to elderly patients >85 years old. The hazard of a recurrent AMI for patients from the Western part of the country was 40% of the hazard for patients from the South (HR = 0.40; 95% CI [0.18, 0.91]; p = 0.0297).

A higher CCI was associated with an increased hazard of a recurrent AMI (cohort A: HR = 1.09; 95% CI [1.01, 1.16]; p = 0.0212, cohort B: HR = 1.13; 95% CI [1.05, 1.22]; p = 0.0009; cohort C: HR = 1.11; 95% CI [1.04, 1.19]; p = 0.0024). Among cohort B patients, those with a hospital stay <7 days for the initial AMI episode reported a higher hazard of a recurrent AMI (HR = 1.83; 95% CI [1.01, 3.32]; p = 0.0455), when compared to patients with a week or longer hospital stay. Among cohort A patients, the hazard of a recurrent AMI for those with a PCI procedure performed during the initial AMI hospitalization was 49% of the hazard for patients that did not have the procedure performed during the initial AMI hospitalization (HR = 0.49; 95% CI [0.28, 0.84]; p = 0.0099).

Table X Model 3: Predictors of the hazard of a recurrent AMI

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.48	[0.24, 0.97]	0.0397*	0.60	[0.29, 1.22]	0.1572	0.59	[0.30, 1.16]	0.1242
71 - 75 years	0.54	[0.28, 1.03]	0.0597	0.49	[0.23, 1.03]	0.0601	0.48	[0.25, 0.93]	0.0302*
76 - 80 years	0.50	[0.25, 0.99]	0.0470*	0.50	[0.24, 1.02]	0.0552	0.43	[0.21, 0.88]	0.0203*
81 - 85 years	0.65	[0.34, 1.24]	0.1904	1.06	[0.56, 2.01]	0.8668	0.86	[0.46, 1.61]	0.6314
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.10	[0.69, 1.76]	0.6767	1.12	[0.68, 1.82]	0.6641	1.15	[0.72, 1.82]	0.5597
Female	Ref			Ref			Ref		
Ethnicity									
White	1.32	[0.62, 2.83]	0.4732	1.82	[0.71, 4.67]	0.211	0.86	[0.43, 1.71]	0.6649
Other	1.04	[0.33, 3.29]	0.9518	1.90	[0.53, 6.82]	0.3237	0.53	[0.16, 1.75]	0.2953
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.84	[0.47, 1.50]	0.5572	0.89	[0.47, 1.69]	0.7172	0.64	[0.33, 1.22]	0.1713
Midwest	0.67	[0.39, 1.17]	0.1619	0.77	[0.44, 1.36]	0.3675	0.67	[0.39, 1.16]	0.1485
West	0.40	[0.18, 0.91]	0.0297*	0.63	[0.28, 1.38]	0.2429	0.75	[0.37, 1.49]	0.4040
South	Ref			Ref			Ref		
CCI	1.09	[1.01, 1.16]	0.0212*	1.13	[1.05, 1.22]	0.0009*	1.11	[1.04, 1.19]	0.0024*
Length of Hospital Stay									
< 7 days	1.15	[0.69, 1.91]	0.5889	1.83	[1.01, 3.32]	0.0455*	1.38	[0.81, 2.32]	0.2335
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.43	[0.16, 1.16]	0.0971	0.71	[0.26, 1.97]	0.5152	0.66	[0.25, 1.80]	0.4202

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.49	[0.28, 0.84]	0.0099*	0.59	[0.34, 1.01]	0.0548	0.68	[0.41, 1.14]	0.1411
Prior Angina	1.44	[0.80, 2.60]	0.2231	1.15	[0.58, 2.30]	0.6897	1.50	[0.84, 2.70]	0.1742
Prior CAD	1.10	[0.67, 1.81]	0.7115	0.93	[0.55, 1.55]	0.7739	1.17	[0.71, 1.93]	0.5436
Prior Therapy									
Prior Statin Therapy,	0.83	[0.51, 1.33]	0.4290	1.11	[0.67, 1.83]	0.6804	1.20	[0.75, 1.93]	0.4536
Prior β-blocker Therapy	1.35	[0.84, 2.17]	0.2134	1.40	[0.84, 2.33]	0.2004	1.48	[0.91, 2.39]	0.1137
Prior ACEI/ARB Therapy	0.92	[0.56, 1.51]	0.7476	1.18	[0.70, 1.98]	0.5329	0.80	[0.49, 1.31]	0.3753
TIME-VARYING PREDICTORS									
Number of office/outpatient visits	1.00	[0.98, 1.02]	0.9813	0.99	[0.97, 1.02]	0.6353	1.00	[0.98, 1.03]	0.6992
Hospitalization visit (any cause)	1.09	[0.47, 2.52]	0.8477	0.86	[0.31, 2.39]	0.7658	1.16	[0.54, 2.51]	0.7061
Emergency room visit (any cause)	1.13	[0.56, 2.26]	0.7391	1.22	[0.57, 2.58]	0.6092	1.11	[0.55, 2.18]	0.7912
Receipt of PCI and/or CABG	1.43	[0.30, 6.70]	0.6516	1.86	[0.37, 9.24]	0.4507	0.64	[0.08, 5.02]	0.6728
Presence of claim related to risk factors	1.31	[0.72, 2.41]	0.3796	1.05	[0.58, 1.92]	0.8657	0.96	[0.55, 1.67]	0.8925
Presence of claim related to low-survival rate conditions	0.85	[0.47, 1.55]	0.4970	0.93	[0.48, 1.80]	0.8317	0.93	[0.51, 1.70]	0.8028
Number of unique prescription claims	1.02	[0.96, 1.09]	0.4594	1.03	[0.96, 1.10]	0.4635	1.00	[0.94, 1.06]	0.9519
Part D coverage gap	1.07	[0.67, 1.71]	0.7752	1.02	[0.62, 1.68]	0.9473	1.03	[0.65, 1.62]	0.9006
Out-of-pocket Medicare costs†	1.00	[0.96, 1.03]	0.7845	1.00	[0.96, 1.04]	0.9457	1.00	[0.98, 1.02]	0.9010
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.61	[0.38, 0.97]	0.0366*	0.61	[0.35, 1.08]	0.0921	0.62	[0.36, 1.06]	0.0809
Not on therapy	—	—	—	0.87	[0.46, 1.64]	0.6658	0.75	[0.41, 1.39]	0.3642
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									
Adherent	1.14	[0.62, 2.10]	0.6819	1.09	[0.65, 1.85]	0.7440	0.98	[0.54, 1.77]	0.9474

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Not on therapy	1.12	[0.59, 2.11]	0.7350	—	—	—	0.88	[0.47, 1.65]	0.6932
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.26	[0.70, 2.27]	0.4410	1.17	[0.63, 2.17]	0.6266	1.57	[0.93, 2.68]	0.0942
Not on therapy	0.85	[0.45, 1.61]	0.6130	0.87	[0.44, 1.71]	0.6862	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

†Costs were divided by 100

Mortality. Table XI presents the results of a discrete-event time model estimating the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of death after accounting for time-varying covariates. Time-varying adherence to statins was not significantly associated with the hazard of mortality (HR = 0.89; 95% CI [0.63, 1.27]; $p = 0.5243$); neither was time-varying adherence to β-blockers (HR = 0.85; 95% CI [0.59, 1.21]; $p = 0.3638$), nor ACEI/ARBs (HR = 0.98; 95% CI [0.70, 1.38]; $p = 0.9260$).

Increasing age was associated with a higher hazard of mortality across all three cohorts. Patients aged 65-70 years (cohort A: HR = 0.35; 95% CI [0.21, 0.60]; $p < .0001$, cohort B: HR = 0.23; 95% CI [0.13, 0.41]; $p < .0001$, cohort C: HR = 0.38; 95% CI [0.23, 0.63], $p = 0.0002$), 71-75 years (cohort A: HR = 0.38; 95% CI [0.23, 0.62]; $p = 0.0001$, cohort B: HR = 0.26; 95% CI [0.16, 0.45]; $p < .0001$, cohort C: HR = 0.35; 95% CI [0.22, 0.55]; $p < .0001$), 76-80 years (cohort A: HR = 0.45; 95% CI [0.28, 0.73]; $p = 0.0014$, cohort B: HR = 0.29; 95% CI [0.18, 0.47]; $p < .0001$, cohort C: HR = 0.45; 95% CI [0.29, 0.69]; $p = 0.0003$), and 81-85 (cohort B: HR = 0.60; 95% CI [0.39, 0.92]; $p = 0.0196$) years had a lower hazard of death in comparison to the elderly patients (> 85 years).

The hazard of death increased significantly with CCI (cohort A: HR = 1.08; 95% CI [1.03, 1.13]; $p = 0.0017$, cohort B: HR = 1.06; 95% CI [1.01, 1.13]; $p = 0.0326$, cohort C: HR = 1.06; 95% CI [1.01, 1.11]; $p = 0.0133$). Patients that had a CABG procedure performed during their initial AMI hospitalization event had a lower hazard of death, with reference to patients that did not have the procedure performed (cohort A: HR = 0.29; 95% CI [0.12, 0.68]; $p = 0.0023$, cohort B: HR = 0.31; 95% CI [0.14, 0.69]; $p = 0.0041$, cohort C: HR = 0.29; 95% CI [0.12, 0.68]; $p = 0.0046$). Similarly, a PCI procedure during the initial AMI hospitalization lowered the

Table XI Model 3: Predictors of the hazard of death

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.35	[0.21, 0.60]	<.0001*	0.23	[0.13, 0.41]	<.0001*	0.38	[0.23, 0.63]	0.0002*
71 - 75 years	0.38	[0.23, 0.62]	0.0001*	0.26	[0.16, 0.45]	<.0001*	0.35	[0.22, 0.55]	<.0001*
76 - 80 years	0.45	[0.28, 0.73]	0.0014*	0.29	[0.18, 0.47]	<.0001*	0.45	[0.29, 0.69]	0.0003*
81 - 85 years	0.68	[0.44, 1.06]	0.0858	0.60	[0.39, 0.92]	0.0196*	0.72	[0.48, 1.08]	0.1133
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.23	[0.88, 1.72]	0.2348	1.36	[0.96, 1.94]	0.0868	1.09	[0.79, 1.51]	0.6042
Female	Ref			Ref			Ref		
Ethnicity									
White	1.05	[0.64, 1.71]	0.8593	1.06	[0.61, 1.83]	0.8481	0.94	[0.59, 1.47]	0.7732
Other	1.05	[0.51, 2.15]	0.9003	0.92	[0.40, 2.11]	0.8434	0.73	[0.35, 1.49]	0.3839
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.78	[0.50, 1.22]	0.2799	0.85	[0.54, 1.36]	0.5045	0.76	[0.50, 1.17]	0.2129
Midwest	0.96	[0.65, 1.43]	0.8415	0.78	[0.53, 1.17]	0.2274	0.79	[0.54, 1.15]	0.2185
West	0.76	[0.46, 1.28]	0.3094	0.67	[0.38, 1.20]	0.1779	0.87	[0.54, 1.40]	0.5610
South	Ref			Ref			Ref		
CCI	1.08	[1.03, 1.13]	0.0017*	1.06	[1.01, 1.13]	0.0326*	1.06	[1.01, 1.11]	0.0133*
Length of Hospital Stay									
< 7 days	1.06	[0.74, 1.50]	0.7611	1.07	[0.74, 1.54]	0.7176	0.93	[0.68, 1.28]	0.6522
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.29	[0.13, 0.64]	0.0023*	0.31	[0.14, 0.69]	0.0041*	0.29	[0.12, 0.68]	0.0046*

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.32	[0.20, 0.50]	<.0001*	0.32	[0.20, 0.52]	<.0001*	0.37	[0.24, 0.56]	<.0001*
Prior Angina	1.05	[0.66, 1.68]	0.8340	0.71	[0.40, 1.25]	0.2347	1.04	[0.65, 1.65]	0.8796
Prior CAD	0.92	[0.64, 1.33]	0.6505	1.09	[0.76, 1.56]	0.6583	1.06	[0.76, 1.49]	0.7244
Prior Therapy									
Prior Statin Therapy,	0.92	[0.65, 1.31]	0.6571	1.03	[0.71, 1.48]	0.8814	0.88	[0.63, 1.22]	0.4313
Prior β-blocker Therapy	0.78	[0.56, 1.10]	0.1548	1.23	[0.87, 1.76]	0.2431	0.74	[0.54, 1.01]	0.0556
Prior ACEI/ARB Therapy	1.26	[0.88, 1.80]	0.2098	1.20	[0.83, 1.72]	0.3387	1.69	[1.17, 2.44]	0.0054*
TIME-VARYING PREDICTORS									
Number of office/outpatient visits	1.01	[1.00, 1.02]	0.0133*	1.02	[1.00, 1.03]	0.0079*	1.01	[1.00, 1.02]	0.2038
Hospitalization visit (any cause)	2.40	[1.54, 3.76]	0.0001*	1.76	[1.06, 2.90]	0.0282*	2.13	[1.40, 3.25]	0.0004*
Emergency room visit (any cause)	2.06	[1.37, 3.10]	0.0005*	1.40	[0.91, 2.17]	0.1290	1.67	[1.12, 2.49]	0.0128*
Receipt of PCI and/or CABG	0.18	[0.02, 1.30]	0.0888	0.52	[0.12, 2.24]	0.3835	0.17	[0.02, 1.26]	0.0824
Presence of claim related to risk factors	0.78	[0.51, 1.19]	0.2429	0.77	[0.50, 1.17]	0.2218	0.80	[0.55, 1.16]	0.2311
Presence of claim related to low-survival rate conditions	1.28	[0.88, 1.87]	0.2029	1.38	[0.91, 2.08]	0.1290	1.44	[1.00, 2.06]	0.0515
Number of unique prescription claims	1.03	[0.99, 1.07]	0.1397	1.04	[1.00, 1.09]	0.0506	1.05	[1.01, 1.08]	0.0147*
Part D coverage gap	0.99	[0.71, 1.38]	0.9285	1.19	[0.85, 1.68]	0.3178	0.93	[0.68, 1.26]	0.6432
Out-of-pocket Medicare costs†	1.00	[0.99, 1.01]	0.8100	1.02	[1.00, 1.03]	0.0139*	1.00	[0.99, 1.02]	0.8517
Recurrent AMI	0.54	[0.19, 1.53]	0.2472	0.47	[0.15, 1.55]	0.2163	0.54	[0.19, 1.50]	0.2348
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.89	[0.63, 1.27]	0.5243	1.08	[0.68, 1.71]	0.7408	1.04	[0.68, 1.61]	0.8453
Not on therapy	—	—	—	1.70	[1.06, 2.73]	0.0274*	1.62	[1.04, 2.53]	0.0320*
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Adherent	0.96	[0.61, 1.49]	0.8493	0.85	[0.59, 1.21]	0.3638	0.86	[0.56, 1.31]	0.4788
Not on therapy	1.00	[0.64, 1.56]	0.9870	—	—	—	0.92	[0.61, 1.39]	0.6883
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.04	[0.68, 1.61]	0.8437	1.07	[0.69, 1.67]	0.7605	0.98	[0.70, 1.38]	0.9260
Not on therapy	1.03	[0.65, 1.63]	0.8892	0.99	[0.62, 1.57]	0.9527	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

†Costs were divided by 100.

hazard of death for patients, when compared to not having the procedure (cohort A: HR = 0.32; 95% CI [0.20, 0.50]; $p < .0001$, cohort B: HR = 0.32; 95% CI [0.20, 0.52]; $p < .0001$, cohort C: HR = 0.37; 95% CI [0.24, 0.56]; $p < .0001$). Cohort C patients that were on ACEI/ARB therapy prior to the initial AMI episode had a higher hazard of death, when compared to those that were not on prior ACEI/ARB therapy (HR = 1.69; 95% CI [1.17, 2.44]; $p = 0.0054$).

The hazard of death increased, corresponding to an increase in the number of office/outpatient visits in each quarter (cohort A: HR = 1.01; 95% CI [1.00, 1.02]; $p = 0.0133$, cohort B: HR = 1.02; 95% CI [1.00, 1.03]; $p = 0.0079$). Patients that had a hospitalization episode in an observed quarter had a significantly higher hazard of death (cohort A: HR = 2.40; 95% CI [1.54, 3.76]; $p = 0.0001$, cohort B: HR = 1.76; 95% CI [1.06, 2.90]; $p = 0.0282$, cohort C: HR = 2.13; 95% CI [1.40, 3.25]; $p = 0.0004$), when compared to patients that did not experience a hospitalization event in that quarter. Similarly, having an emergency room event in a quarter increased the hazard of death (cohort A: HR = 2.06; 95% CI [1.37, 3.10]; $p = 0.0005$, cohort C: HR = 1.67; 95% CI [1.12, 2.49]; $p = 0.0128$), with reference to not having such an episode. Among cohort C patients, an increase in the number of unique prescriptions per quarter increased the risk of death (HR = 1.05; 95% CI [1.01, 1.08]; $p = 0.0147$). Higher out-of-pocket Medicare costs increased the hazard of death among cohort B patients (HR = 1.02; 95% CI [1.00, 1.03]; $p = 0.0139$).

Among cohorts B and C, a higher hazard of death was observed among patients that were not on concomitant statin therapy, when compared to those that were not adherent to their concomitant statin therapy (cohort B: HR = 1.70; 95% CI [1.06, 2.73]; $p = 0.0274$, cohort C: HR = 1.62; 95% CI [1.04, 2.53]; $p = 0.0320$).

The results of continuous time models (model 3b) estimating the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of subsequent outcomes, accounting for time-varying covariates, are presented in Appendix C – Additional Results, Tables XXV and XXVI.

Model 4: Marginal structural model

Across the observed person-quarters for cohort A, the average stabilized weight was 5.08 (±89.38) and median was 0.97 (Table XII). For cohort B the average stabilized weight was 17.94 (±379.45) with median weight 0.96. Finally, for cohort C the average stabilized weight was 81.78 (±3,097.91) with a median of 0.96 and range of 241,123.83.

Table XII Stabilized weights

	Stabilized Weights				
	Person Quarters	Mean	Std. Dev.	Median	Range
Cohort A (Statin Therapy)	8,497	5.08	89.38	0.97	5,409.55
Cohort B (β-blocker Therapy)	7,920	17.94	379.45	0.96	20,074.42
Cohort C (ACEI/ARB Therapy)	7,832	81.78	3,097.91	0.96	241,123.83

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Figure IV displays the temporal distribution of the log of stabilized weights in cohort A. Similarly, Figures V and VI display the temporal distribution of the log of stabilized weights in cohorts B and C, respectively.

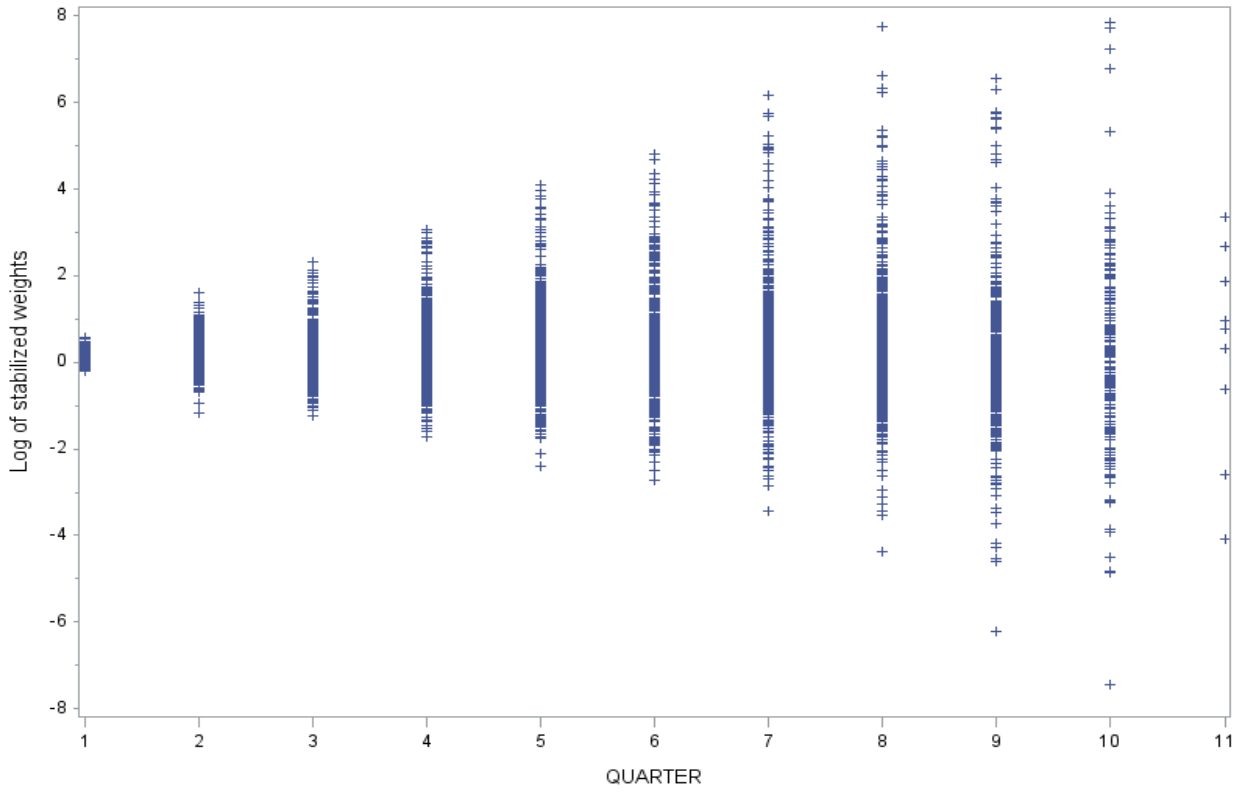

Figure IV Log of stabilized weights across quarters in cohort A (statin therapy)

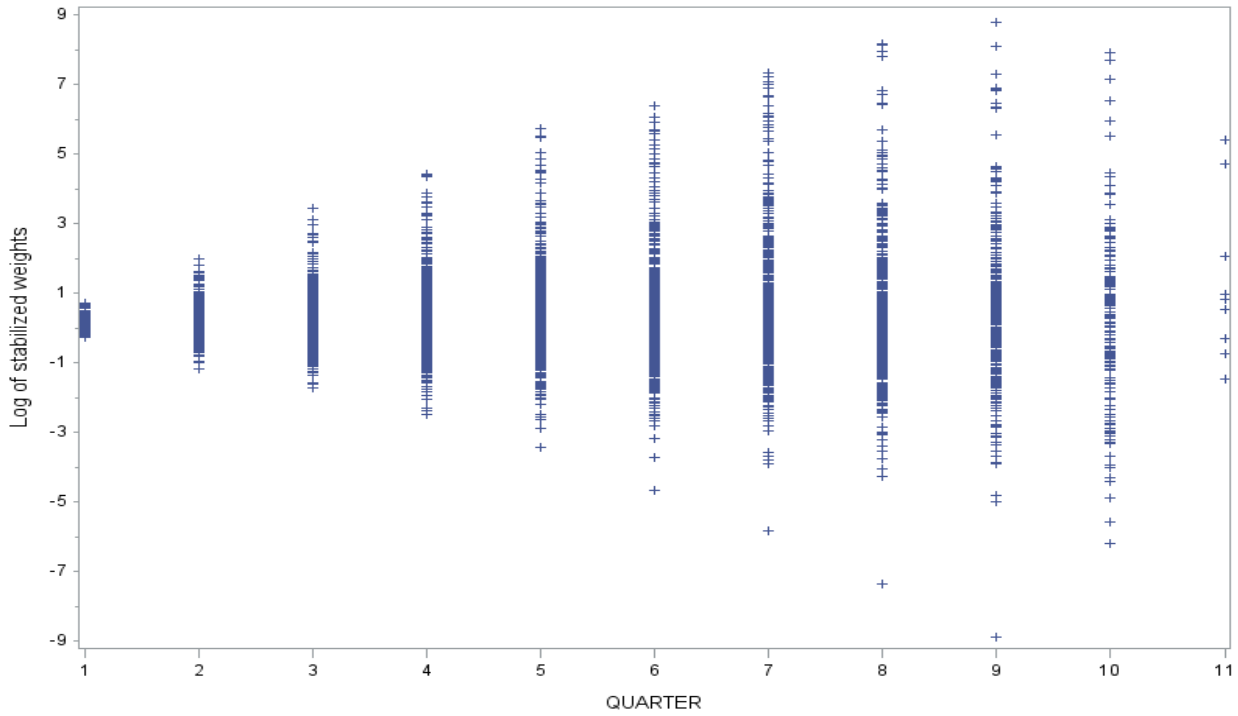

Figure V Log of stabilized weights across quarters in cohort B (β-blocker therapy)

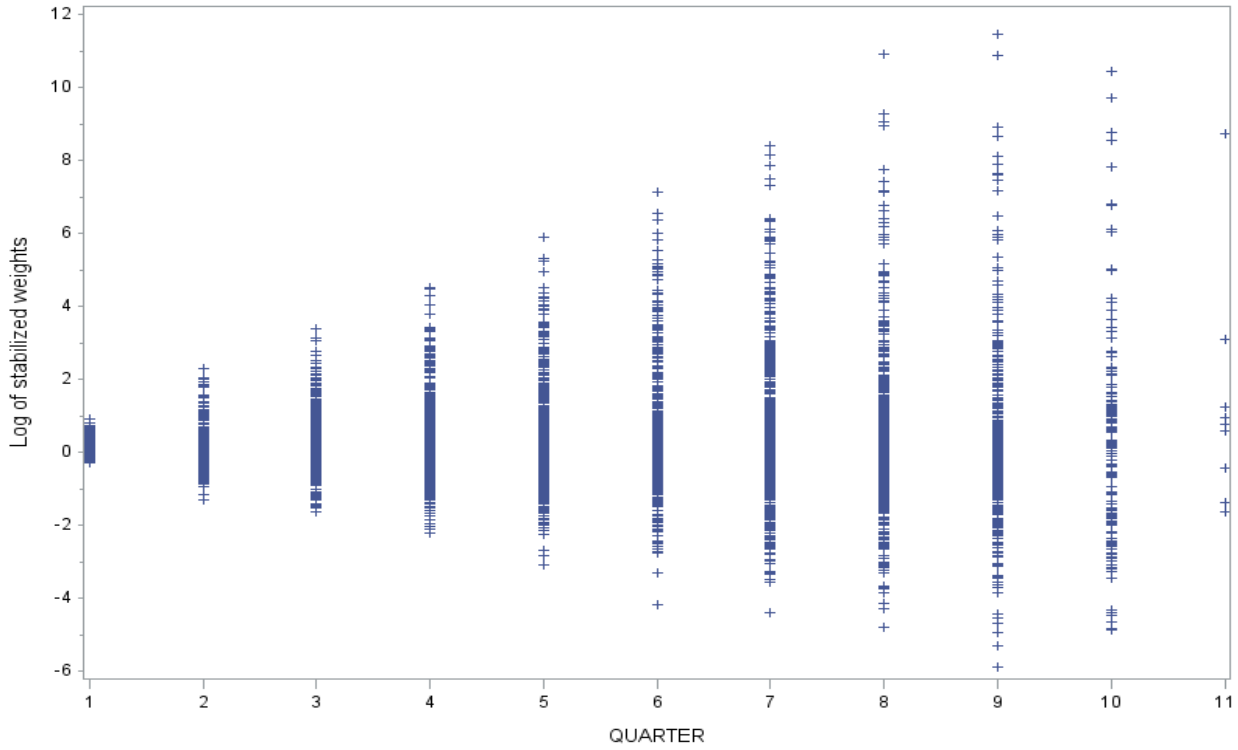

Figure VI Log of stabilized weights across quarters in cohort C (ACEI/ARB therapy)

The adjusted HRs from MSMs estimating the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of subsequent outcomes are presented in Table XIII.

Table XIII Model 4: Adjusted hazard ratios (HRs) from marginal structural models (MSMs)

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
RECURRENT AMI									
Statin Adherence	0.64	[0.36, 1.15]	0.1370						
β-blocker Adherence				0.75	[0.43, 1.33]	0.3270			
ACEI/ARB Adherence							1.19	[0.55, 2.61]	0.6566
MORTALITY									
Statin Adherence	0.91	[0.58, 1.43]	0.6772						
β-blocker Adherence				0.71	[0.40, 1.25]	0.2322			
ACEI/ARB Adherence							1.64	[0.78, 3.47]	0.1193

*$p<0.05$

HR, Hazards Ratio; AMI, acute myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Refer to Appendix C – Additional Results for the distribution of normalized weights across all quarters for all three study cohorts (Table XXVII, Figures X, XI, and XII) and adjusted HRs from MSMs using normalized weights (Table XXVIII), to estimate the effect of time-varying adherence to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of subsequent outcomes.

Aim 4: Comparison of Predictive Values of Adherence Measured as a Time-varying and Time-invariant Variable

The adjusted HRs from various models discussed above, estimating the effect of adherence (time-varying and time-invariant) to statin, β-blocker, and ACEI/ARB therapy in cohorts A, B, and C, respectively, on the risk of subsequent outcomes are presented in Table XIV. Statin adherence, measured as varying over 90 day periods, was associated with a lower risk of a recurrent AMI in discrete-event time models 2 (baseline covariates + time-varying adherence) and 3 (baseline covariates + time-varying adherence + time-varying covariates) in cohort A. When accounting only for baseline covariates (model 2), the hazard for a recurrent AMI among statin adherent patients in cohort A was 63% of the hazard among non-adherent patients (HR = 0.63; 95% CI [0.40, 0.99]; $p = 0.0471$). When accounting for baseline covariates and time-varying covariates (model 3), the hazard for a recurrent AMI among statin adherent patients in cohort A was 61% of the hazard among non-adherent patients (HR = 0.61, 95% CI [0.38, 0.97]; $p = 0.0366$).

Table XV presents model fits statistics for the various models fit to the data. Discrete-event time models (2 and 3) have the best model fit statistics across all three cohorts while estimating the effect of adherence of subsequent outcomes. On the other hand, MSMs displayed the worst fit statistics.

Table XIV Adjusted HRs estimating the effect of adherence on subsequent outcomes across various models

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
RECURRENT AMI									
Model 1	0.73	[0.47, 1.15]	0.1707	0.95	[0.59, 1.54]	0.8435	0.98	[0.61, 1.58]	0.9381
Model 2	0.63	[0.40, 0.99]	0.0471*	1.12	[0.67, 1.89]	0.6622	1.57	[0.93, 2.67]	0.0931
Model 3	0.61	[0.38, 0.97]	0.0366*	1.09	[0.65, 1.85]	0.7440	1.57	[0.93, 2.68]	0.0942
Model 4	0.64	[0.36, 1.15]	0.1370	0.75	[0.43, 1.33]	0.3270	1.19	[0.55, 2.61]	0.6566
MORTALITY									
Model 1	0.73	[0.53, 1.00]	0.0531	1.21	[0.86, 1.71]	0.2704	1.04	[0.75, 1.44]	0.8215
Model 2	0.86	[0.61, 1.21]	0.3913	0.97	[0.68, 1.38]	0.8469	1.04	[0.74, 1.46]	0.8189
Model 3	0.89	[0.63, 1.27]	0.5243	0.85	[0.59, 1.21]	0.3638	0.98	[0.70, 1.38]	0.9260
Model 4	0.91	[0.58, 1.43]	0.6772	0.71	[0.40, 1.25]	0.2322	1.64	[0.78, 3.47]	0.1193

*$p<0.05$

HR, Hazards Ratio; AMI, acute myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model

Table XV Model fit statistics

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	-2 Log L	AIC	BIC	-2 Log L	AIC	BIC	-2 Log L	AIC	BIC
RECURRENT AMI									
Model 1	1123.78	1167.78	1221.78	995.82	1039.82	1091.67	1120.9	1164.90	1219.15
Model 2	836.44	884.44	943.34	763.35	811.35	867.91	838.10	886.097	945.28
Model 3	833.56	899.56	980.56	761.75	827.75	905.52	837.16	903.16	984.54
Model 4	2069.40	2109.40	2158.48	8335.92	8375.92	8423.05	3690.06	3730.06	3779.374
MORTALITY									
Model 1	2072.58	2116.58	2184.77	1955.52	1999.52	2066.89	2351.63	2395.63	2466.95
Model 2	1392.38	1440.38	1514.77	1286.02	1334.02	1407.52	1516.26	1564.26	1624.06
Model 3	1321.18	1389.18	1494.58	1224.95	1292.95	1397.08	1461.62	1529.62	1639.84
Model 4	3342.77	3382.77	3444.76	7891.38	7931.38	7992.63	6407.54	6447.54	6512.38

-2 Log L, -2 log likelihood; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; AMI, acute myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model

Sensitivity Analysis

Adjusted HRs estimating the effect of adherence on subsequent outcomes in cohort A at different cut-offs for defining patients as adherent (40% and 90%), across the various models are reported in Table XVI. Similarly, Tables XVII and XVIII present the adjusted HRs in cohorts B and C, respectively.

Table XVI Sensitivity analysis - cohort A (statin therapy)

	Adherence cut-offs					
	40%			90%		
	HR	95% CI	*p*	HR	95% CI	*p*
RECURRENT AMI						
Model 1	0.75	[0.41, 1.40]	0.3693	0.81	[0.53, 1.26]	0.3534
Model 2	0.65	[0.42, 1.02]	0.0632	0.65	[0.42, 1.02]	0.0632
Model 3	0.64	[0.40, 1.01]	0.0524	0.64	[0.40, 1.01]	0.0524
Model 4	0.77	[0.33, 1.82]	0.5484	0.72	[0.39, 1.33]	0.2965
MORTALITY						
Model 1	0.86	[0.55, 1.37]	0.5291	0.73	[0.53, 1.00]	0.0487*
Model 2	0.70	[0.47, 1.03]	0.0671	0.88	[0.63, 1.23]	0.4500
Model 3	0.65	[0.44, 0.97]	0.0341*	0.88	[0.63, 1.23]	0.4654
Model 4	0.72	[0.40, 1.31]	0.2879	0.59	[0.33, 1.05]	0.0748

*$p<0.05$
HR, Hazards Ratio; AMI, acute myocardial infarction;
Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model

Table XVII Sensitivity analysis - cohort B (β-blocker therapy)

	Adherence cut-offs					
	40%			90%		
	HR	95% CI	*p*	HR	95% CI	*p*
RECURRENT AMI						
Model 1	1.65	[0.70, 3.90]	0.2539	1.00	[0.63, 1.57]	0.9837
Model 2	1.09	[0.66, 1.80]	0.7364	1.09	[0.66, 1.80]	0.7364
Model 3	1.07	[0.64, 1.77]	0.8020	1.07	[0.64, 1.77]	0.8020
Model 4	1.00	[0.54, 1.87]	0.9955	0.97	[0.54, 1.73]	0.9157

	Adherence cut-offs					
	40%			90%		
	HR	95% CI	*p*	HR	95% CI	*p*
MORTALITY						
Model 1	1.85	[1.05, 3.26]	0.0342*	1.04	[0.75, 1.43]	0.8191
Model 2	1.04	[0.67, 1.63]	0.8486	1.11	[0.78, 1.58]	0.5555
Model 3	0.85	[0.55, 1.34]	0.4927	0.99	[0.70, 1.41]	0.9475
Model 4	0.38	[0.19, 0.77]	0.0075*	1.05	[0.60, 1.84]	0.8642

*$p<0.05$

HR, Hazards Ratio; AMI, acute myocardial infarction;
Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model

Table XVIII Sensitivity analysis - cohort C (ACEI/ARB therapy)

	Adherence cut-offs					
	40%			90%		
	HR	95% CI	*p*	HR	95% CI	*p*
RECURRENT AMI						
Model 1	1.06	[0.57, 2.00]	0.8514	1.22	[0.77, 1.92]	0.4010
Model 2	1.60	[0.97, 2.66]	0.0678	1.60	[0.97, 2.66]	0.0678
Model 3	1.61	[0.97, 2.68]	0.0656	1.61	[0.97, 2.68]	0.0656
Model 4	1.50	[0.40, 5.58]	0.5439	1.48	[0.60, 3.67]	0.3941
MORTALITY						
Model 1	1.27	[0.77, 2.08]	0.3537	1.19	[0.88, 1.62]	0.2612
Model 2	1.38	[0.89, 2.13]	0.1481	1.02	[0.73, 1.41]	0.9222
Model 3	1.30	[0.84, 2.00]	0.2425	0.99	[0.72, 1.37]	0.9526
Model 4	2.02	[0.70, 5.88]	0.1966	0.97	[0.57, 1.67]	0.9155

*$p<0.05$

HR, Hazards Ratio; AMI, acute myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker
Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model

CHAPTER 5

DISCUSSION AND CONCLUSION

This study explores the relationship between long-term adherence to secondary prevention therapies post-AMI and subsequent outcomes, specifically, recurrent AMI and mortality, using the 5% Medicare random national sample data 2006 - 2008. Using a retrospective cohort study design, estimates of the causal effect of time-invariant and time-varying measures of adherence to statin, β-blocker and ACEI/ARB therapy post-AMI on the risk of a recurrent AMI and mortality are reported, using various statistical models. Estimates from MSMs accounting for time-dependent confounding have also been reported.

Among cohort A patients, 60.71% were found to be adherent to their statin therapy over the first year post-AMI. Similarly, 61.39% and 56.05% were found to be adherent to β-blocker (cohort B) and ACEI/ARB (cohort C) therapy, respectively. Studies have documented a wide range of adherence and compliance rates to these drug classes post-AMI (Benner et al. 2002; Kramer et al., 2006; Schneeweiss, Patirck, Maclure, Dormuth, & Glynn, 2007; Simpson et al., 2003). However, different definitions of adherence/compliance, different time periods of measurement, and widely differing populations make it extremely essential that these statistics be compared with caution. Rasmussen et al. (2007) measured adherence to statins, β-blockers and calcium channel blockers over a period of one year post-AMI among the elderly and categorized patients with proportion of days covered (PDC) ≥80% as adherent; 80.5% and 73.5% were documented to be adherent to statin and β-blocker therapy, respectively. The study was

conducted on a population based in Ontario, which has different health insurance policies for prescription medications for the elderly (Jackevius et al., 2002), among other differences, which could have led to the higher reported adherence rates. This does, however, pose an important question on our current policies governing prescription medication insurance for the elderly such as the 'donut hole' and its impact on adherence and subsequent outcomes. The adherence estimates are comparable to the summary estimate of 57% for adherence to primary and secondary prevention therapies provided by a recent meta-analysis of observational studies (Naderi et al., 2012). Patients who had at least 75% of days covered for a specific drug over a specified time period were classified as adherent in the meta-analysis.

Age emerged as a statistically significant predictor of adherence to β-blocker therapy, however, the same was not observed for adherence to statin or ACEI/ARB therapy. Among cohort B patients, >85 year olds were less likely to adhere to β-blocker therapy. Possible reasons could be increasingly complex drug regimens which also lead to lack of sufficient funds with the elderly approaching the 'donut hole' in their Part D prescription coverage and widowhood (Osterberg, & Blaschke, 2005; Schneeweiss et al., 2007; Zhang, Donohue, Lave, O'Donnell, & Newhouse, 2009). The study reported females to more likely be adherent to β-blocker therapy than males, however, gender was not a significant predictor of adherence to statin or ACEI/ARB therapy. Although this relationship between gender and β-blocker therapy adherence has been documented elsewhere (Gislason et al., 2006); this finding is not consistent across studies. White patients were more likely to be adherent to statin therapy in comparison to Black patients. This relationship has been supported previously in the literature (Monane et al., 1996; Sharkness, & Snow, 1992), with possible reasons cited being differences in health-related beliefs and socioeconomic status. Differences in socioeconomic status could also be the underlying

explanation for patients in the Northeast being more likely to adhere to β-blocker therapy than patients residing in the South of US. However, none of the demographic factors emerged as statistically significant predictors of adherence across all three cohorts. The reported associations between these factors and medication adherence in the literature have been inconsistent (Avorn et al., 1998; Balkrishnan, 1998; Kulkarni, Alexander, Lytie, Heiss, & Peterson, 2006; Monane et al., 1997). Prior therapy with statins was associated with significantly higher adherence post-AMI to statins. This association was also observed for β-blocker and ACEI/ARB therapy. Rasmussen et al.'s (2007) population-based, observational study of elderly AMI survivors in Ontario reported the same finding, suggesting medication use preceding index AMI hospitalization improves adherence to these medication regimens post-AMI.

Patients that are comparatively older during their initial AMI and those with a severe comorbid profile were more likely to suffer a recurrent episode. Increasing age and CCI were also associated with a higher hazard of death. Additionally, patients from the West have a lower hazard of a recurrent AMI when compared to patients from the South. This can be explained via the higher obesity rates and higher prevalence of risk factors of CVD among the southern population (Roger et al., 2012). However, recent data from the Centers for Disease Control and Prevention National Environmental Public Health Tracking Network has reported that age-adjusted acute myocardial infarction hospitalization rates are the highest in the Northeastern states (Talbott et al., 2013). The risk of a recurrent AMI and mortality was found to be lower among patients that had a PCI performed during their initial hospitalization, which is consistent with prior reports (Chen et al., 2010). A similar association was found between the performance of CABG and the hazard of mortality. Interestingly, patients with a hospitalization stay of <7

days for their initial AMI episode were found to have a higher risk of recurrent AMI. Traditionally, length of hospital stay (LOS) has been associated with severity of disease, whereby a longer LOS would imply higher severity. Such patients would therefore be more likely to be readmitted. However, with hospitals aggressively trying to decrease LOS, excessive LOS reduction, especially for certain conditions may be harmful because discharge before medical stability may result in increased hospital readmission rates. Patients on ACEI/ARB therapy prior to the initial AMI were found to have a higher hazard of mortality across all models. Patients that are on ACEI/ARB therapy prior to initial AMI probably have a different comorbidity/severity profile that may explain the higher hazard of mortality among such patients.

A significant contribution of this study is the finding that patients that are not on statin therapy among the ACEI/ARB and β-blocker users had an approximately 60% higher hazard of death when compared to patients that were not adherent to statin therapy. This result was reported across models with and without time-varying predictors. Since the end-point here was all cause mortality and not just cardiovascular mortality this finding supports the various studies that have been published recently on the various beneficial pleiotropic effects of statins (Endres, 2006; Ganotakis, Mikhailidis, & Vardas, 2006; Lokhandwala, West-Strum, Banahan, Bentley & Yang, 2012; Paraskevas, Tzovaras, Briana, & Mikhailidis, 2007). Statins have been shown to improve endothelial dysfunction, increase nitric oxide bioavailability, have antioxidant properties, inhibit inflammatory responses, and stabilize atherosclerotic plaques (Davignon, 2004). Although prior studies have demonstrated the beneficial effects of statin beyond its cardiovascular effects, this study adds significantly to that by suggesting that not being on statins

is much worse than not being adherent to them. A similar effect was not observed for ACEI/ARBs or β-blockers.

The presence of a hospitalization visit in a quarter was associated with an increased hazard of death across all three study cohorts. Further, the number of office/outpatient visits, presence of an ER visit, number of unique prescription claims and out-of pocket Medicare costs were found to increase the hazard of death. However, these results were observed in one or two of the study cohorts, but not across cohorts A, B, and C. All of the above mentioned variables can be used as indicators of disease severity and hence their association with an increased hazard of death is not surprising.

A statistically significant protective effect of long-term adherence on subsequent outcomes was only observed among statin users where adherence was measured as a time-varying covariate. The hazard of a recurrent AMI among patients adherent to statin was 63% (HR = 0.63; 95% CI [0.40, 0.99]; $p = 0.0471$) that of non-adherent patient when only baseline covariates were included in the model. On including time-varying covariates, the hazard of a recurrent AMI for adherent patients dropped to 61% of that for non-adherent patients (HR = 0.61, 95% CI [0.38, 0.97]; $p = 0.0366$). A statistically significant protective effect of long-term adherence to β-blockers on subsequent outcomes was not observed. Similarly, long-term adherence to ACEI/ARBs did not have a statistically significant protective effect against recurrent AMI or mortality in this study. Additionally, most of the hazard ratios for the effect of long-term adherence to ACEI/ARBs on subsequent outcomes across all models were found to be above 1, suggesting an opposite effect, although not statistically significant.

The results from the MSMs for the effect of long-term adherence to secondary prevention therapies post-AMI on subsequent outcomes were not statistically significant. The hazard ratios from the MSMs were found to be less than 1, for the effect of adherence to statins and β-blockers on both subsequent outcomes, i.e., recurrent AMI and all-cause mortality. However, this was not true for the effect of adherence to ACEI/ARBs on subsequent outcomes.

When comparing the hazard ratios across all models for the effect of long-term adherence to statin therapy on recurrent AMI (Figure VII) and all-cause mortality (Figure VIII), it is interesting to note that the protective effect of adherence to statin on recurrent AMI seems to become stronger across the models 1 through 4. The reverse trend is observed for the effect of adherence to statins on all-cause mortality. However, these results are not statistically significant, and therefore should be interpreted with caution.

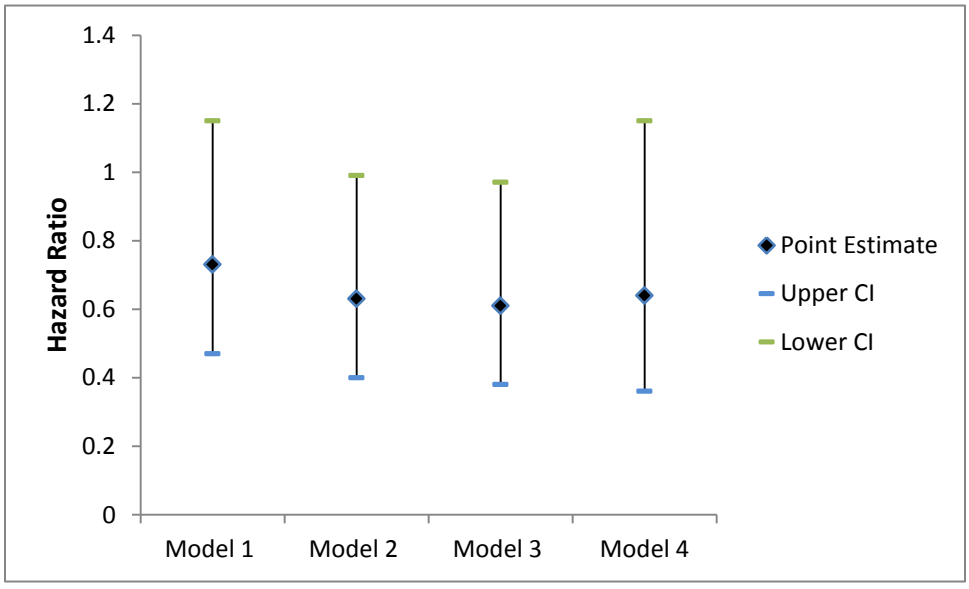

Figure VII Adjusted hazard ratios estimating the effect of statin adherence (cohort A) on recurrent AMI. Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model.

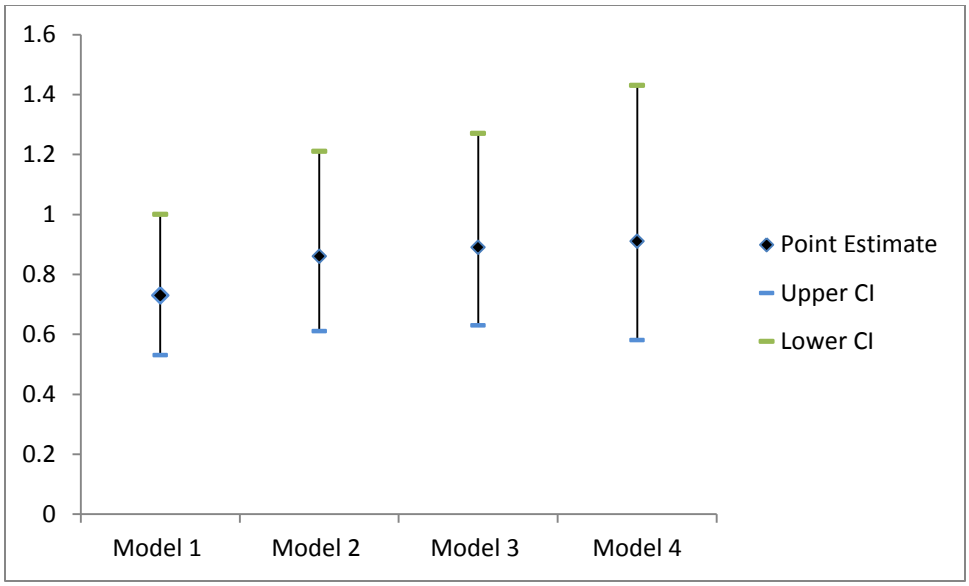

Figure VIII Adjusted hazard ratios estimating the effect of statin adherence (cohort A) on mortality. Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model.

Models 2 and 3, i.e., the models with time-varying adherence with and without time-varying predictors were found to have the best goodness-of-fit statistics. A possible reason for the observed results from the MSMs and poor goodness-of-fit could be the comparatively higher variability of the stabilized weights. The recent study by Yu et al. (2010) shows the application of MSMs over conventional models, where the protective effect of adherence to hypoglycemics was only observed with MSMs. However, combining all patient-quarters, the mean of the stabilized weights in their study was 1.37(±19.57) and median 0.81. In comparison, the mean of the stabilized weights across all patient-quarters in this study for cohort A was 5.08 (±89.38) and median 0.97. The mean and standard deviation of stabilized weights for cohorts B and C were much higher. Very few patients were observed through all 11 quarters, which could lead to highly variable weights.

In order to reduce the variability of the weights in each risk set over time, normalized weights were computed and used in estimation of the MSMs (Xiao et al., 2010). Combining all patient-quarters, the standard deviation of the normalized weights was 4.36 for cohort A and the observed median was 0.67. For cohorts B and C the standard deviation of the normalized weights was 5.09 and 6.46, respectively, with a median of 0.44 and 0.43, respectively. Using normalized weights in the estimation of MSMs, long-term adherence to statin was associated with a statistically significant reduction in the hazard of a recurrent AMI (HR =0.60; 95% CI [0.37, 0.95]; $p = 0.0312$).

The consistency of the IPTW estimator relies on the positivity assumption (Neugebauer, & van der Laan, 2005; Wang, Petersen, Bangsberg, & van der Laan, 2006; Cole, & Hernan, 2008). Essentially, each subject should have a positive probability of being exposed to each level of treatment, i.e., being adherent or non-adherent in our study population. This assumption can be practically violated when the subjects in a subgroup with a particular combination of covariates have an extremely low probability of being adherent, that they were in fact adherent will lead to them being assigned large weights (Xiao, Moodie, & Abrahamowicz, 2013). These weights get magnified by the multiplication of the probabilities over the follow-up time, leading to instability of the estimator. Normalized weights can be used to reduce the variability of the weights. However, when the covariate-treatment association is very strong this might still lead to issues in estimation. In such cases other approaches have been proposed in the literature to deal with estimation issues arising from highly variable weights. These include (i) truncation of weights (Kish, 1992; Wang et al., 2006; Bembom, & van der Laan, 2008a; Cole, & Hernan, 2008; Moore, Neugebauer, & van der Laan, 2009), (ii) G-computation (van der Wal, Prins, Lumbreras, & Geskus, 2009), (iii) exclusion of certain covariates that lead to high covariate-

treatment association but are weakly associated with the outcome (Bembom, & van der Laan, 2008b), (iv) 'trimming', i.e., exclusion of observations that lead to issues (LaLonde, 1986; Heckman, Ichimura, & Todd, 1998; Dehejia, & Wahba; 1999; Crump, Hotz, Imbens, & Mitnik, 2006), and (v) history-restricted MSMs where a limited portion of the treatment history is used for MSM estimation (Neugebauer, et al., 2007). The utilization of these approaches with the present data should be evaluated for future research.

In addition to the variability of the weights, this research has several limitations that need to be acknowledged. The study uses observational data for analysis. This could lead to errors due to misclassification resulting from coding errors while claims processing. Adherence was computed using prescription claim data. The presence of a claim for a drug does not necessarily imply that the drug was administered. However, previous studies have shown that observational data provide a good tool for conducting adherence studies. Further, adherence in the study period was dichotomized at the 80% mark into adherent and non-adherent categories to make interpretation easier and intuitive. However, sensitivity analyses were conducted using different cutoff points, so as to corroborate the conclusions. An interesting finding of the sensitivity analyses was that patients on β-blockers when classified as adherent at a cut-off of 40% were found to have a 38% (HR = 0.38; 95% CI [0.19, 0.77]; $p = 0.0075$) hazard of mortality when compared to non-adherent patients via MSM estimators. The results of the model estimating the effect of time-invariant β-blocker adherence on the hazard of mortality suggested a detrimental effect of being adherent (HR = 1.85; 95% CI [1.05, 3.26]; $p = 0.0342$). Figure IX shows the results of models 2 and 3 too, in addition to the above results. These results mirror the effect documented by Yu et al. (2010). They estimated the effects of medication adherence to hypoglycemics on the risk of micro vascular complications in type 2 diabetes patients. The Cox

models with time-invariant and time-varying adherence measures, and after accounting for time-varying covariates, presented a detrimental effect of higher adherence. The estimates from MSM, however, suggested that higher medication adherence may results in a reduced risk of micro vascular complications among patients with type 2 diabetes. The covariate-treatment association is most likely weaker when adherence to β-blockers is cut-off at 40%, thus, explaining the results of the sensitivity analysis. This also implies that reduced adherence to β-blockers does have an impact on the hazard of mortality; patients are better off having less than perfect adherence than being completely off the drug.

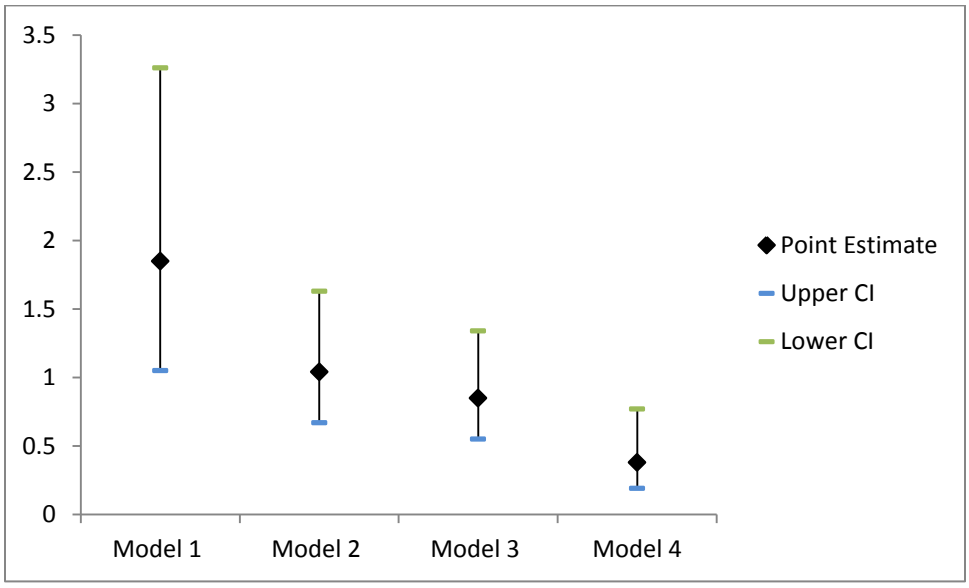

Figure IX Adjusted hazard ratios estimating the effect of β-blocker adherence (cohort B) on mortality when adherence is cut-off at 40%. Model 1: Time-invariant adherence; Model 2: Baseline covariates + time-varying adherence; Model 3: Baseline covariates + time-varying predictors + time-varying adherence; Model 4: Marginal structural model.

Another limitation is the population of the study. The study was conducted among elderly AMI patients. Given their higher baseline cardiovascular risk and lower tolerance to multiple medication regimes, they are the most vulnerable population. These variations in baseline cardiovascular risk and compliance profiles may alter the magnitude of association

between adherence and subsequent outcomes; hence the results should be extended to other age groups with caution. Using cardiovascular mortality as the end-point, rather than all-cause mortality would have led to richer results. Unfortunately, data on the cause of death was not available.

One of the assumptions necessary for causal inference using MSMs is the presence of no unmeasured confounders. Although, the relevant literature has been thoroughly scanned to include potential predictors, there are certain risk factors such as smoking, low-density lipoprotein levels, body weight, and blood pressure that are not measurable using observational data. In addition over-the-counter medication use (for e.g., aspirin) cannot be tracked. Information on adverse reactions, allergies, or intolerance, all of which are associated with medication discontinuation was not available. Observational data does, however, offer considerable advantages in terms of feasibility and more observation points for cheaper. Perhaps future studies can investigate feasible ways of acquiring information on the additional covariates for use with those considered in the study.

This study only estimates the effect of long-term adherence to secondary prevention therapies on recurrent AMI and mortality. Future studies can investigate this relationship using different outcomes, such as costs. This research question can be explored using different data such as MarketScan Commercial and Medicare, in order to avoid problems arising from few patients followed for the entire length of time. The benefits of using MSMs over other statistical techniques, or the benefits of using time-varying measures of adherence versus time-invariant measures can be further investigated among a different population with a different condition. The time-varying nature of adherence can also be investigated by studying the rate of change of adherence over time. The effect of various factors on the rate of change can be estimated using

multilevel models. Exploring adherence as a time-varying measure offers a wide range of avenues for future research.

This study documents adherence rates to secondary prevention therapies post-AMI in the Medicare population, as well as healthcare utilization rates in terms of hospitalizations, ER, and office visits over three-month windows. This study also contributes significantly from a methodological perspective. Different statistical models have been compared while measuring adherence as time-invariant and time-varying. Time-dependent confounding has also been accounted for. There is a lack of studies estimating the effect of long-term adherence to secondary prevention therapies on subsequent outcomes while accounting for time-dependent confounding. It is imperative to understand this relationship with the clinical and economic burden of cardiovascular diseases being relatively high among Americans. With observational studies being the most pragmatic way of studying this relationship, it is essential to better our methodology to approach the research question under consideration. This study is a step in that direction. There are not many studies where the results do not suggest MSMs as the superior approach to handle time-dependent confounding issues. However, it is important to note here that publication bias could be an explanation, as studies that do not find differences between standard methods and MSMs probably do not get published. Taking note of this, further studies are required to understand if MSMs should be the preferred methodology when exploring the relationship between long-term medication adherence and health outcomes.

In conclusion, the purpose of this study was to estimate the effect of long-term adherence to secondary prevention therapies post-AMI on subsequent cardiovascular outcomes. Time-invariant and time-varying measures of adherence were computed. A longitudinal cohort observational study design was employed using the retrospective Medicare 5% random national

sample claims data from January 1st, 2006 to December 31st, 2008. Estimates of the effect of adherence from Cox regression models and MSMs were compared, along with model-fit-statistics. Adherence to statin therapy, measured as varying over time was associated with a reduced risk of a recurrent AMI in the discrete-event time models. However, the results for the effect of adherence to β-blockers and ACEI/ARBs on subsequent cardiovascular events were not statistically significant. Further studies are required to better understand if MSMs should be the preferred methodology when exploring the relationship between long-term medication adherence and health outcomes.

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APPENDICES

APPENDIX-A

ICD-9-CM CODES

Table XIX ICD-9-CM diagnosis and procedure codes

Condition	ICD-9-CM Diagnosis and Procedure Codes
Acute Myocardial Infarction	*410.x0, 410.x1*
Angina	*413.xx*
Asthma	*439.xx*
Cancer	*140.xx – 172.xx, 174-198.xx, 199.1, 200.xx-208.xx*
Cerebrovascular Disease	*430.xx – 438.xx*
Chronic Kidney Disease	*403.xx, 404.xx, 582.xx, 583.xx, 585.xx, 586.xx, 588.xx*
Chronic Obstructive Pulmonary Disease	*491.20, 491.21, 492.0x, 492.8x, 496.xx, 518.1x, 518.2x, 506.4x*
Congestive Heart Failure	*428.xx*
Coronary Artery Bypass Graft Surgery	*36.10-36.19*
Coronary Artery Disease	*414.xx*
Diabetes	*250.xx*
Dyslipidemia	*272.0x – 272.4x*
Hypertension	*401.xx*
Partial AV Block	*426.0x, 426.12, 426.13, 426.2x – 426.4x, 426.51 – 426.54, 426.7*
Percutaneous Coronary Intervention	*36.01-36.09*
Peripheral Vascular Disease	*443.9x, 785.4x, v43.4x, 411.xx*
Sinus Bradycardia	*427.81*

APPENDIX-B

LIST OF DRUGS

β-Blocker Medications

- acebutolol HCL
- atenolol
- betaxolol HCL
- bisoprolol fumarate
- carteolol HCL
- carvedilol
- labetalol HCL
- metoprolol succinate
- metoprolol tartrate
- nadolol
- nebivolol HCL
- penbutolol sulfate
- pindolol
- propranolol HCL
- timolol maleate

β-Blocker Combination Products

- atenolol & chlorthalidone
- bisoprolol & HCTZ
- nadolol & bendroflumethiazide
- metoprolol & HCTZ
- propranolol & HCTZ
- timolol & HCTZ

Statin Medications

- lovastatin
- rosuvastatin
- fluvastatin
- atorvastatin
- pravastatin
- simvastatin

Statin Combination Products

- niacin & lovastatin
- atorvastatin & amlodipine
- niacin & simvastatin

- pravastatin & aspirin
- ezetimibe & simvastatin

ARB Medications

- candesartan
- eprosartan
- irbesartan
- losartan
- olmesartan
- telmisartan
- valsartan

ACEI Medications

- benazepril
- captopril
- enalapril
- fosinopril
- lisinopril
- moexipril
- perindopril
- quinapril
- ramipril
- trandolopril

ACEI Combination Products

- amlodipine & benazepril
- benazepril & HCTZ
- captopril & HCTZ
- enalapril & HCTZ
- enalapril & felodipine
- fosinopril & HCTZ
- lisinopril & HCTZ
- moexipril & HCTZ
- lisinopril & nutritional supplement
- quinapril & HCTZ
- trandolopril-verapamil HCL

ARB Combination Products

- candesartan & HCTZ
- eprosartan & HCTZ
- telmisartan & amlodipine
- irbesartan & HCTZ
- losartan & HCTZ
- amlodipine & olmesartan
- olmesartan & HCTZ
- telmisartan & HCTZ
- aliskiren & valsartan
- valsartan & HCTZ
- amlodipine & valsartan
- amlodipine & valsartan & HCTZ

APPENDIX-C

ADDITIONAL RESULTS

Table XXa Time-varying predictors for subjects in cohort A (statin therapy)

	Quarters Observed											
	1		2		3		4		5		6	
	N = 1,091		N = 1,091		N = 1,057		N = 1,030		N = 1,008		N = 977	
Adherent to statin therapy, *n (%)*	838	76.81	805	73.79	739	69.91	703	68.25	678	67.26	651	66.63
Number of office/outpatient visits, *mean (SD)*	16.58	13.58	11.88	12.28	10.25	10.20	9.72	10.39	9.63	11.51	9.44	10.40
Hospitalization visit (any cause), *n (%)*	144	13.20	83	7.61	67	6.34	48	4.66	46	4.56	42	4.3
Emergency room visit (any cause), *n (%)*	185	16.96	123	11.27	104	9.84	88	8.54	82	81.3	80	8.19
Receipt of PCI and/or CABG, n (%)	55	5.04	17	1.56	9	0.85	5	0.49	9	0.89	11	1.13
Presence of claim related to risk factors, *n (%)*	957	87.72	852	78.09	778	73.60	748	72.62	712	70.63	712	72.88
Presence of claim related to low-survival rate conditions, *n (%)*	190	17.42	180	16.50	156	14.76	136	13.20	142	14.09	146	14.94
Number of unique prescription claims, *mean (SD)*	10.09	4.12	8.30	4.09	7.96	4.01	8.02	4.17	7.76	4.02	7.67	4.03
Part D coverage gap, *n (%)*	323	29.61	410	37.58	461	43.61	416	40.39	360	35.71	325	33.27
Out of pocket Medicare costs, *mean (SD)*	538.97	638.73	549.29	693.86	512.62	611.37	486.67	593.53	475.63	1,106.17	448.90	623.65
Recurrent AMI, *n (%)*	–	–	19	1.74	14	1.32	16	1.55	16	1.59	13	1.33

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Table XXb Time-varying predictors for subjects in cohort A (statin therapy)

	Quarters Observed									
	7		8		9		10		11	
	N = 960		N = 688		N = 400		N = 186		N = 9	
Adherent to statin therapy, *n (%)*	641	66.77	456	66.28	274	68.50	121	65.05	5	55.56
Number of office/outpatient visits, *mean (SD)*	8.61	10.23	7.84	13.81	7.34	11.57	4.66	6.96	0.22	0.44
Hospitalization visit (any cause), *n (%)*	46	4.79	26	3.78	11	2.75	4	2.15	0	0.00
Emergency room visit (any cause), *n (%)*	72	7.50	38	5.52	19	4.75	7	3.76	0	0.00
Receipt of PCI and/or CABG, n (%)	9	0.94	6	0.87	1	0.25	1	0.54	0	0.00
Presence of claim related to risk factors, *n (%)*	606	63.13	408	59.3	218	54.50	79	42.47	0	0.00
Presence of claim related to low-survival rate conditions, *n (%)*	131	13.65	90	13.08	44	11.00	11	5.91	0	0.00
Number of unique prescription claims, *mean (SD)*	7.12	4.21	6.69	4.27	6.59	4.09	5.49	4.33	1.11	1.62
Part D coverage gap, *n (%)*	320	33.33	271	39.39	177	44.25	82	44.09	4	44.44
Out of pocket Medicare costs, *mean (SD)*	385.70	566.82	324.74	570.83	323.69	498.37	196.02	370.02	21.97	33.99
Recurrent AMI, *n (%)*	14	1.46	6	0.87	0	0.00	1	0.54	0	0.00

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Table XXIa Time-varying predictors for subjects in cohort B (β-blocker therapy)

	Quarters Observed											
	1		2		3		4		5		6	
	N = 1,021		N = 1,020		N = 984		N = 955		N = 930		N = 907	
Adherent to β-blocker therapy, *n (%)*	782	76.59	704	69.02	654	66.46	614	64.29	603	64.84	593	65.38
Number of office/outpatient visits, *mean (SD)*	15.87	12.97	11.27	11.39	9.59	9.27	9.00	9.88	9.16	10.51	8.66	9.93
Hospitalization visit (any cause), *n (%)*	134	13.12	72	7.06	66	6.71	37	3.87	45	4.84	35	3.86
Emergency room visit (any cause), *n (%)*	164	16.06	112	10.98	79	8.03	74	7.75	69	7.42	60	6.62
Receipt of PCI and/or CABG, n (%)	52	5.09	17	1.67	10	1.02	4	0.42	12	1.29	10	1.10
Presence of claim related to risk factors, *n (%)*	901	88.25	780	76.47	726	73.78	690	72.25	660	70.97	647	71.33
Presence of claim related to low-survival rate conditions, *n (%)*	163	15.96	151	14.80	136	13.82	112	11.73	123	13.23	117	12.90
Number of unique prescription claims, *mean (SD)*	9.61	3.83	7.83	3.75	7.49	3.73	7.53	3.77	7.31	3.70	7.34	3.64
Part D coverage gap, *n (%)*	268	26.25	336	32.94	414	42.07	372	38.95	311	33.44	275	30.32
Out of pocket Medicare costs, *mean (SD)*	519.43	643.85	512.97	631.85	505.13	875.43	451.20	529.84	425.70	543.63	414.82	567.92
Recurrent AMI, *n (%)*	–	–	19	1.86	14	1.42	12	1.26	16	1.72	9	0.99

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Table XXIb Time-varying predictors for subjects in cohort B (β-blocker therapy)

	Quarters Observed									
	7		8		9		10		11	
	N = 893		N = 652		N = 381		N = 168		N = 9	
Adherent to β-blocker therapy, *n (%)*	581	65.06	422	64.72	256	67.19	115	68.45	6	66.67
Number of office/outpatient visits, *mean (SD)*	8.35	10.21	7.17	8.23	7.06	11.74	4.56	6.94	0.33	0.50
Hospitalization visit (any cause), *n (%)*	37	4.14	29	4.45	9	2.36	3	1.79	0	0.00
Emergency room visit (any cause), *n (%)*	68	7.61	37	5.67	20	5.25	8	4.76	0	0.00
Receipt of PCI and/or CABG, n (%)	8	0.90	4	0.61	1	0.26	1	0.60	0	0.00
Presence of claim related to risk factors, *n (%)*	564	63.16	389	59.66	211	55.38	76	45.24	1	11.11
Presence of claim related to low-survival rate conditions, *n (%)*	111	12.43	80	12.27	40	10.50	11	6.55	0	0.00
Number of unique prescription claims, *mean (SD)*	6.78	3.96	6.46	3.93	6.08	3.81	5.13	4.08	1.44	1.81
Part D coverage gap, *n (%)*	273	30.57	248	38.04	165	43.31	75	44.64	5	55.56
Out of pocket Medicare costs, *mean (SD)*	377.37	550.30	313.46	439.95	291.03	432.73	177.32	351.55	15.69	29.79
Recurrent AMI, *n (%)*	10	1.12	9	1.38	1	0.26	2	1.19	0	0.00

SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Table XXIIa Time-varying predictors for subjects in cohort C (ACEI/ARB therapy)

	Quarters Observed											
	1		2		3		4		5		6	
	N = 1,025		N = 1,025		N = 984		N = 948		N = 921		N = 889	
Adherent to ACEI/ARB therapy, *n (%)*	771	75.22	748	72.98	683	69.41	623	65.72	585	63.52	549	61.75
Number of office/outpatient visits, *mean (SD)*	16.5	14.03	11.9	12.48	10.30	10.83	9.66	11.12	9.74	11.77	9.12	10.39
Hospitalization visit (any cause), *n (%)*	145	14.15	90	8.78	71	7.22	48	5.06	51	5.54	41	4.61
Emergency room visit (any cause), *n (%)*	173	16.88	132	12.88	93	9.45	87	9.18	85	9.23	78	8.77
Receipt of PCI and/or CABG, n (%)	48	4.68	18	1.76	10	1.02	5	0.53	8	0.87	10	1.12
Presence of claim related to risk factors, *n (%)*	903	88.10	800	78.05	733	74.49	689	72.68	646	70.14	653	73.45
Presence of claim related to low-survival rate conditions, *n (%)*	165	16.10	153	14.93	130	13.21	111	11.71	123	13.36	126	14.17
Number of unique prescription claims, *mean (SD)*	10.22	4.15	8.44	4.08	8.04	4.05	8.12	4.10	7.88	4.06	7.80	3.95
Part D coverage gap, *n (%)*	327	31.90	378	36.88	448	45.53	400	42.19	338	36.70	305	34.31
Out of pocket Medicare costs, *mean (SD)*	520.05	654.91	541.08	678.91	514.90	630.72	482.21	598.59	476.71	1,131.42	455.81	629.62
Recurrent AMI, *n (%)*	–	–	22	2.15	12	1.22	14	1.48	20	2.17	14	1.57

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Table XXIIb Time-varying predictors for subjects in cohort C (ACEI/ARB therapy)

	Quarters Observed									
	7		8		9		10		11	
	N = 874		N = 627		N = 366		N = 164		N = 9	
Adherent to ACEI/ARB therapy, *n (%)*	521	59.61	360	57.42	212	57.92	97	59.15	4	44.44
Number of office/outpatient visits, *mean (SD)*	8.45	9.98	7.22	8.51	7.08	11.23	4.32	5.36	0.22	0.44
Hospitalization visit (any cause), *n (%)*	45	5.15	36	5.74	8	2.19	3	1.83	0	0.00
Emergency room visit (any cause), *n (%)*	67	7.67	34	5.42	17	4.64	6	3.66	0	0.00
Receipt of PCI and/or CABG, n (%)	10	1.14	6	0.96	1	0.27	2	1.22	0	0.00
Presence of claim related to risk factors, *n (%)*	551	63.04	368	58.69	205	56.01	78	47.56	1	1.11
Presence of claim related to low-survival rate conditions, *n (%)*	110	12.59	76	12.12	39	10.66	11	6.71	0	0.00
Number of unique prescription claims, *mean (SD)*	7.17	4.32	6.74	4.26	6.54	4.13	5.53	4.26	1.67	1.73
Part D coverage gap, *n (%)*	311	35.58	257	40.99	175	47.81	72	43.90	6	66.67
Out of pocket Medicare costs, *mean (SD)*	388.62	571.93	328.60	468.64	323.40	497.35	185.57	341.48	23.01	33.34
Recurrent AMI, *n (%)*	11	1.26	9	1.44	2	0.55	2	1.22	0	0.00

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; SD, standard deviation; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; AMI, acute myocardial infarction

Table XXIII Model 2b: Predictors of the hazard of a recurrent AMI

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.49	[0.25, 0.98]	0.0441*	0.57	[0.28, 1.16]	0.1198	0.58	[0.29, 1.14]	0.1157
71 - 75 years	0.55	[0.29, 1.04]	0.0674	0.47	[0.22, 0.99]	0.0458*	0.48	[0.25, 0.92]	0.0262*
76 - 80 years	0.51	[0.26, 1.00]	0.0499*	0.47	[0.23, 0.97]	0.0397*	0.42	[0.21, 0.85]	0.0163*
81 - 85 years	0.65	[0.34, 1.24]	0.1929	0.99	[0.52, 1.89]	0.9858	0.86	[0.46, 1.61]	0.6287
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.05	[0.66, 1.66]	0.8446	1.10	[0.68, 1.79]	0.6923	1.15	[0.73, 1.82]	0.5529
Female	Ref			Ref			Ref		
Ethnicity									
White	1.25	[0.59, 2.65]	0.5598	1.78	[0.70, 4.52]	0.2282	0.85	[0.43, 1.69]	0.6490
Other	1.03	[0.33, 3.28]	0.9563	1.88	[0.53, 6.74]	0.3316	0.53	[0.16, 1.74]	0.2926
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.80	[0.45, 1.43]	0.4512	0.86	[0.45, 1.63]	0.6412	0.62	[0.33, 1.18]	0.1485
Midwest	0.65	[0.37, 1.12]	0.1178	0.74	[0.42, 1.29]	0.2851	0.66	[0.38, 1.15]	0.1431
West	0.39	[0.17, 0.89]	0.0253*	0.60	[0.27, 1.31]	0.1963	0.71	[0.36, 1.43]	0.3398
South	Ref			Ref			Ref		
CCI	1.09	[1.03, 1.16]	0.0051*	1.14	[1.07, 1.22]	<.0001*	1.12	[1.06, 1.19]	0.0002*
Length of Hospital Stay									
< 7 days	1.12	[0.68, 1.86]	0.6514	1.83	[1.01, 3.31]	0.0462*	1.33	[0.79, 2.24]	0.2795
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.41	[0.16, 1.11]	0.0795	0.68	[0.25, 1.85]	0.4438	0.64	[0.24, 1.73]	0.3839

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.47	[027, 0.81]	0.0060*	0.57	[0.33, 0.98]	0.0413*	0.65	[0.40, 1.08]	0.0937
Prior Angina	1.47	[0.82, 2.63]	0.1963	1.11	[0.55, 2.21]	0.7735	1.47	[0.82, 2.62]	0.1915
Prior CAD	1.13	[0.69, 1.86]	0.6280	0.96	[0.57, 1.60]	0.8682	1.19	[0.72, 1.97]	0.4881
Prior Therapy									
Prior Statin Therapy,	0.84	[0.53, 1.35]	0.4756	1.13	[0.69, 1.85]	0.6385	1.18	[0.74, 1.89]	0.4933
Prior β-blocker Therapy	1.36	[0.85, 2.19]	0.1996	1.39	[0.83, 2.31]	0.2078	1.49	[0.92, 2.40]	0.1062
Prior ACEI/ARB Therapy	0.93	[0.57, 1.53]	0.7837	1.16	[0.69, 1.94]	0.5735	0.78	[0.48, 1.27]	0.3225
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.67	[0.43, 1.06]	0.0871	0.69	[0.39, 1.20]	0.1901	0.68	[0.40, 1.15]	0.1478
Not on therapy	—	—	—	0.95	[0.51, 1.79]	0.8808	0.82	[0.45, 1.52]	0.5307
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									
Adherent	1.25	[0.68, 2.31]	0.4720	1.19	[0.70, 2.01]	0.5231	1.00	[0.55, 1.79]	0.9858
Not on therapy	1.19	[0.63, 2.24]	0.5971	—	—	—	0.89	[0.47, 1.67]	0.7080
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.34	[0.75, 2.39]	0.3235	1.29	[0.70, 2.38]	0.4189	1.68	[0.99, 2.84]	0.0528
Not on therapy	0.85	[0.45, 1.60]	0.6099	0.91	[0.46, 1.77]	0.7698	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

Table XXIV Model 2b: Predictors of the hazard of death

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.43	[0.26, 0.71]	0.0011*	0.25	[0.15, 0.44]	<.0001*	0.41	[0.25, 0.68]	0.0005*
71 - 75 years	0.43	[0.27, 0.70]	0.0006*	0.29	[0.17, 0.49]	<.0001*	0.37	[0.23, 0.59]	<.0001*
76 - 80 years	0.50	[0.31, 0.80]	0.0043*	0.30	[0.19, 0.49]	<.0001*	0.44	[0.28, 0.68]	0.0002*
81 - 85 years	0.69	[0.44, 1.07]	0.0938	0.62	[0.41, 0.96]	0.0305*	0.74	[0.50, 1.11]	0.1484
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.24	[0.89, 1.73]	0.2004	1.38	[0.98, 1.94]	0.0672	1.14	[0.83, 1.58]	0.4147
Female	Ref			Ref			Ref		
Ethnicity									
White	0.93	[0.57, 1.51]	0.7607	1.06	[0.61, 1.82]	0.8424	0.83	[0.53, 1.30]	0.4090
Other	0.94	[0.46, 1.94]	0.8727	0.92	[0.41, 2.09]	0.8435	0.61	[0.30, 1.25]	0.1759
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.74	[0.47, 1.15]	0.1745	0.77	[0.49, 1.21]	0.2584	0.68	[0.44, 1.04]	0.0721
Midwest	0.93	[0.63, 1.38]	0.7328	0.77	[0.52, 1.15]	0.1989	0.75	[0.52, 1.11]	0.1482
West	0.68	[0.41, 1.15]	0.1497	0.59	[0.34, 1.05]	0.0738	0.79	[0.49, 1.27]	0.3362
South	Ref			Ref			Ref		
CCI	1.14	[1.09, 1.19]	<.0001*	1.14	[1.09, 1.20]	<.0001*	1.12	[1.08, 1.17]	<.0001*
Length of Hospital Stay									
< 7 days	0.94	[0.66, 1.32]	0.7014	0.97	[0.68, 1.39]	0.8763	0.82	[0.60, 1.12]	0.2184
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.25	[0.11, 0.56]	0.0008*	0.40	[0.18, 0.85]	0.0174*	0.28	[0.12, 0.65]	0.0032*

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.29	[0.18, 0.46]	<.0001*	0.32	[0.20, 0.51]	<.0001*	0.35	[0.23, 0.53]	<.0001*
Prior Angina	1.05	[0.67, 1.67]	0.8225	0.66	[0.38, 1.16]	0.1501	1.07	[0.68, 1.69]	0.7690
Prior CAD	1.01	[0.70, 1.44]	0.9766	1.19	[0.84, 1.70]	0.3334	1.12	[0.81, 1.56]	0.4896
Prior Therapy									
Prior Statin Therapy,	0.93	[0.66, 1.30]	0.6548	1.11	[0.78, 1.59]	0.5662	0.90	[0.65, 1.25]	0.5279
Prior β-blocker Therapy	0.82	[0.59, 1.15]	0.2490	1.10	[0.78, 1.56]	0.5820	0.77	[0.57, 1.05]	0.1033
Prior ACEI/ARB Therapy	1.26	[0.88, 1.81]	0.2100	1.20	[0.83, 1.73]	0.3243	1.64	[1.14, 2.37]	0.0077*
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.91	[0.65, 1.28]	0.5942	1.11	[0.71, 1.74]	0.6385	1.13	[0.74, 1.74]	0.5714
Not on therapy	—	—	—	1.70	[1.07, 2.73]	0.0261*	1.69	[1.08, 2.63]	0.0204*
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									
Adherent	1.07	[0.69, 1.67]	0.7533	1.04	[0.73, 1.48]	0.8314	0.96	[0.63, 1.45]	0.8284
Not on therapy	1.15	[0.73, 1.80]	0.5440	—	—	—	1.06	[0.70, 1.60]	0.7947
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.20	[0.78, 1.84]	0.4019	1.28	[0.82, 2.00]	0.2751	1.18	[0.84, 1.66]	0.3344
Not on therapy	1.03	[0.65, 1.62]	0.9144	1.04	[0.66, 1.65]	0.8571	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

Table XXV Model 3b: Predictors of the hazard of a recurrent AMI

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.45	[0.22, 0.91]	0.0267*	0.54	[0.26, 1.11]	0.0915	0.56	[0.28, 1.11]	0.0953
71 - 75 years	0.51	[0.27, 0.96]	0.0367	0.45	[0.21, 0.95]	0.0353*	0.46	[0.24, 0.88]	0.0196*
76 - 80 years	0.48	[0.24, 0.95]	0.0356*	0.46	[0.23, 0.95]	0.0351*	0.41	[0.20, 0.84]	0.0140*
81 - 85 years	0.63	[0.33, 1.21]	0.1645	1.01	[0.53, 1.92]	0.9832	0.83	[0.44, 1.57]	0.5721
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.11	[0.70, 1.77]	0.6591	1.16	[0.71, 1.89]	0.5651	1.14	[0.72, 1.82]	0.5691
Female	Ref			Ref			Ref		
Ethnicity									
White	1.39	[0.65, 2.99]	0.3940	1.84	[0.72, 4.72]	0.2046	0.88	[0.44, 1.75]	0.7140
Other	1.08	[0.34, 3.44]	0.9001	1.82	[0.50, 6.57]	0.3607	0.55	[0.17, 1.83]	0.3324
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.83	[0.46, 1.48]	0.5245	0.89	[0.47, 1.68]	0.7072	0.65	[0.34, 1.23]	0.1844
Midwest	0.68	[0.39, 1.19]	0.1761	0.78	[0.44, 1.37]	0.3857	0.68	[0.39, 1.18]	0.1690
West	0.40	[0.18, 0.91]	0.0294*	0.62	[0.28, 1.36]	0.2322	0.72	[0.36, 1.44]	0.3488
South	Ref			Ref			Ref		
CCI	1.07	[1.00, 1.15]	0.0561	1.12	[1.04, 1.21]	0.0039*	1.10	[1.02, 1.17]	0.0081*
Length of Hospital Stay									
< 7 days	1.19	[0.72, 1.98]	0.5017	1.85	[1.02, 3.36]	0.0419*	1.38	[0.82, 2.33]	0.2263
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.44	[0.16, 1.18]	0.1018	0.68	[0.25, 1.89]	0.4632	0.64	[0.24, 1.72]	0.3743

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.49	[0.28, 0.85]	0.0105*	0.59	[0.34, 1.02]	0.0587	0.68	[0.41, 1.13]	0.1327
Prior Angina	1.33	[0.74, 2.41]	0.3428	1.08	[0.54, 2.16]	0.8199	1.39	[0.77, 2.52]	0.2705
Prior CAD	1.10	[0.66, 1.81]	0.7176	0.93	[0.56, 1.56]	0.7808	1.16	[0.70, 1.92]	0.5652
Prior Therapy									
Prior Statin Therapy,	0.81	[0.51, 1.31]	0.3949	1.11	[0.68, 1.83]	0.6801	1.16	[0.72, 1.87]	0.5438
Prior β-blocker Therapy	1.34	[0.84, 2.15]	0.2233	1.38	[0.83, 2.29]	0.2115	1.46	[0.90, 2.36]	0.1259
Prior ACEI/ARB Therapy	0.90	[0.55, 1.48]	0.6851	1.11	[0.66, 1.87]	0.6934	0.78	[0.48, 1.27]	0.3214
TIME-VARYING PREDICTORS									
Number of office/outpatient visits	1.01	[0.99, 1.03]	0.5378	1.00	[0.98, 1.03]	0.8509	1.01	[0.99, 1.03]	0.2742
Hospitalization visit (any cause)	1.23	[0.53, 2.86]	0.6351	1.04	[0.37, 2.89]	0.9417	1.19	[0.54, 2.61]	0.6642
Emergency room visit (any cause)	1.22	[0.58, 2.57]	0.5954	1.26	[0.56, 2.84]	0.5846	1.11	[0.54, 2.25]	0.7832
Receipt of PCI and/or CABG	2.56	[0.56, 11.73]	0.2264	2.80	[0.59, 13.34]	0.1975	1.06	[0.14, 8.15]	0.9581
Presence of claim related to risk factors	1.52	[0.83, 2.79]	0.1782	1.20	[0.66, 2.20]	0.5486	1.12	[0.64, 1.95]	0.6923
Presence of claim related to low-survival rate conditions	0.87	[0.48, 1.58]	0.6488	0.91	[0.48, 1.75]	0.7780	0.91	[0.49, 1.66]	0.7508
Number of unique prescription claims	1.05	[0.99, 1.11]	0.1070	1.06	[1.00, 1.13]	0.0628	1.03	[0.97, 1.09]	0.3724
Part D coverage gap	1.00	[0.63, 1.59]	0.9979	0.90	[0.55, 1.48]	0.6823	0.96	[0.61, 1.51]	0.8564
Out of pocket Medicare costs†	0.98	[0.94, 1.03]	0.3810	0.99	[0.94, 1.04]	0.5768	1.00	[0.97, 1.03]	0.7566
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.64	[0.40, 1.02]	0.0617	0.64	[0.36, 1.13]	0.1224	0.66	[0.39, 1.13]	0.1305
Not on therapy	—	—	—	0.95	[0.50, 1.78]	0.8612	0.82	[0.45, 1.52]	0.5339
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									
Adherent	1.15	[0.62, 2.13]	0.6543	1.10	[0.65, 1.87]	0.7223	0.97	[0.54, 1.75]	0.9114

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Not on therapy	1.11	[0.59, 2.11]	0.7488	—	—	—	0.85	[0.45, 1.61]	0.6195
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.31	[0.73, 2.36]	0.3605	1.22	[0.66, 2.26]	0.5282	1.64	[0.97, 2.78]	0.0670
Not on therapy	0.89	[0.47, 1.68]	0.7077	0.92	[0.47, 1.80]	0.8044	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

†Costs were divided by 100

Table XXVI Model 3b: Predictors of the hazard of death

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
BASELINE COVARIATES									
Age									
65 - 70 years	0.34	[0.20, 0.58]	<.0001*	0.23	[0.13, 0.41]	<.0001*	0.36	[0.22, 0.61]	0.0001*
71 - 75 years	0.34	[0.21, 0.56]	<.0001*	0.25	[0.15, 0.43]	<.0001*	0.32	[0.20, 0.51]	<.0001*
76 - 80 years	0.41	[0.25, 0.67]	0.0004*	0.29	[0.18, 0.47]	<.0001*	0.42	[0.27, 0.66]	0.0001*
81 - 85 years	0.65	[0.42, 1.02]	0.0591	0.61	[0.39, 0.94]	0.0247*	0.70	[0.46, 1.04]	0.0782
> 85 years	Ref			Ref			Ref		
Gender									
Male	1.24	[0.89, 1.74]	0.2091	1.39	[0.97, 1.97]	0.0708	1.07	[0.77, 1.48]	0.6837
Female	Ref			Ref			Ref		
Ethnicity									
White	1.07	[0.65, 1.75]	0.7893	1.05	[0.61, 1.81]	0.8708	0.93	[0.59, 1.46]	0.7523
Other	1.16	[0.56, 2.39]	0.6971	0.95	[0.41, 2.19]	0.8963	0.77	[0.38, 1.60]	0.4883
Black	Ref			Ref			Ref		
Region of US									
Northeast	0.79	[0.51, 1.24]	0.3134	0.85	[0.53, 1.35]	0.4842	0.77	[0.50, 1.19]	0.2354
Midwest	0.97	[0.65, 1.43]	0.8580	0.80	[0.54, 1.19]	0.2694	0.79	[0.53, 1.16]	0.2191
West	0.76	[0.46, 1.28]	0.3038	0.70	[0.40, 1.25]	0.2285	0.89	[0.55, 1.44]	0.6373
South	Ref			Ref			Ref		
CCI	1.07	[1.02, 1.13]	0.0066*	1.05	[1.00, 1.12]	0.0708	1.05	[1.00, 1.10]	0.0491*
Length of Hospital Stay									
< 7 days	1.10	[0.77, 1.56]	0.5943	1.06	[0.73, 1.52]	0.7729	0.92	[0.67, 1.27]	0.6190
≥ 7 days	Ref			Ref			Ref		
Surgical Procedure									
CABG	0.31	[0.14, 0.68]	0.0039*	0.30	[0.13, 0.68]	0.0039*	0.27	[0.11, 0.65]	0.0036*

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
PCI	0.31	[0.19, 0.49]	<.0001*	0.33	[0.20, 0.52]	<.0001*	0.37	[0.24, 0.56]	<.0001*
Prior Angina	0.98	[0.61, 1.57]	0.9428	0.71	[0.40, 1.24]	0.2255	0.97	[0.61, 1.55]	0.9125
Prior CAD	0.93	[0.65, 1.34]	0.7009	1.07	[0.74, 1.53]	0.7336	1.09	[0.78, 1.52]	0.6244
Prior Therapy									
Prior Statin Therapy,	0.91	[0.64, 1.29]	0.6027	1.03	[0.72, 1.49]	0.8638	0.86	[0.62, 1.20]	0.3870
Prior β-blocker Therapy	0.79	[0.57, 1.10]	0.1624	1.19	[0.84, 1.69]	0.3255	0.74	[0.54, 1.00]	0.0534
Prior ACEI/ARB Therapy	1.21	[0.84, 1.74]	0.2993	1.18	[0.82, 1.70]	0.3797	1.54	[1.07, 2.22]	0.0210*
TIME-VARYING PREDICTORS									
Number of office/outpatient visits	1.01	[1.01, 1.02]	0.0017*	1.02	[1.00, 1.03]	0.0040*	1.01	[1.00, 1.02]	0.0412*
Hospitalization visit (any cause)	2.58	[1.64, 4.05]	<.0001*	1.89	[1.14, 3.16]	0.0145*	2.20	[1.43, 3.40]	0.0004*
Emergency room visit (any cause)	2.36	[1.59, 3.50]	<.0001*	1.62	[1.05, 2.49]	0.0294*	1.89	[1.26, 2.82]	0.0019*
Receipt of PCI and/or CABG	0.47	[0.06, 3.46]	0.4573	1.12	[0.26, 4.79]	0.8770	0.38	[0.05, 2.82]	0.3430
Presence of claim related to risk factors	0.89	[0.58, 1.35]	0.5720	0.88	[0.58, 1.35]	0.5592	0.90	[0.62, 1.32]	0.5977
Presence of claim related to low-survival rate conditions	1.28	[0.87, 1.87]	0.2085	1.36	[0.90, 2.05]	0.1452	1.36	[0.93, 1.97]	0.1097
Number of unique prescription claims	1.06	[1.02, 1.09]	0.0042*	1.08	[1.03, 1.12]	0.0003*	1.07	[1.04, 1.11]	0.0001*
Part D coverage gap	0.88	[0.63, 1.22]	0.4363	1.01	[0.72, 1.42]	0.9394	0.84	[0.62, 1.14]	0.2699
Out of pocket Medicare costs†	1.00	[0.98, 1.01]	0.5687	1.01	[1.00, 1.02]	0.1284	0.99	[0.98, 1.02]	0.5919
Recurrent AMI	0.37	[0.13, 1.03]	0.0579	0.27	[0.08, 0.88]	0.0300*	0.31	[0.11, 0.87]	0.0262*
TIME-VARYING ADHERENCE									
Statin Therapy									
Adherent	0.90	[0.64, 1.28]	0.5542	1.03	[0.66, 1.62]	0.8980	1.06	[0.69, 1.64]	0.7923
Not on therapy	—	—	—	1.64	[1.02, 2.63]	0.0407*	1.70	[1.09, 2.64]	0.0193*
Non-adherent	Ref			Ref			Ref		
β-blocker Therapy									

	Cohort A (Statin Therapy)			Cohort B (β-blocker Therapy)			Cohort C (ACEI/ARB Therapy)		
	N = 1,091			N = 1,021			N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
Adherent	0.91	[0.58, 1.42]	0.6791	0.89	[0.62, 1.28]	0.5295	0.86	[0.57, 1.31]	0.4894
Not on therapy	0.95	[0.61, 1.50]	0.8349	—	—	—	0.89	[0.59, 1.35]	0.5782
Non-adherent	Ref			Ref			Ref		
ACEI/ARB Therapy									
Adherent	1.12	[0.73, 1.71]	0.6182	1.07	[0.68, 1.67]	0.7790	1.08	[0.77, 1.52]	0.6564
Not on therapy	1.11	[0.70, 1.75]	0.6621	1.01	[0.64, 1.61]	0.9660	—	—	—
Non-adherent	Ref			Ref			Ref		

*$p<0.05$

HR, Hazards Ratio; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson comorbidity index; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; CAD, coronary artery disease

†Costs were divided by 100

Table XXVII Normalized weights

	Normalized weights				
	Person Quarters	Mean	Std. Dev.	Median	Range
Cohort A (Statin Therapy)	8,497	1.00	4.36	0.67	219.32
Cohort B (β-blocker Therapy)	7,920	1.00	5.09	0.44	222.44
Cohort C (ACEI/ARB Therapy)	7,832	1.00	6.46	0.43	353.76

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

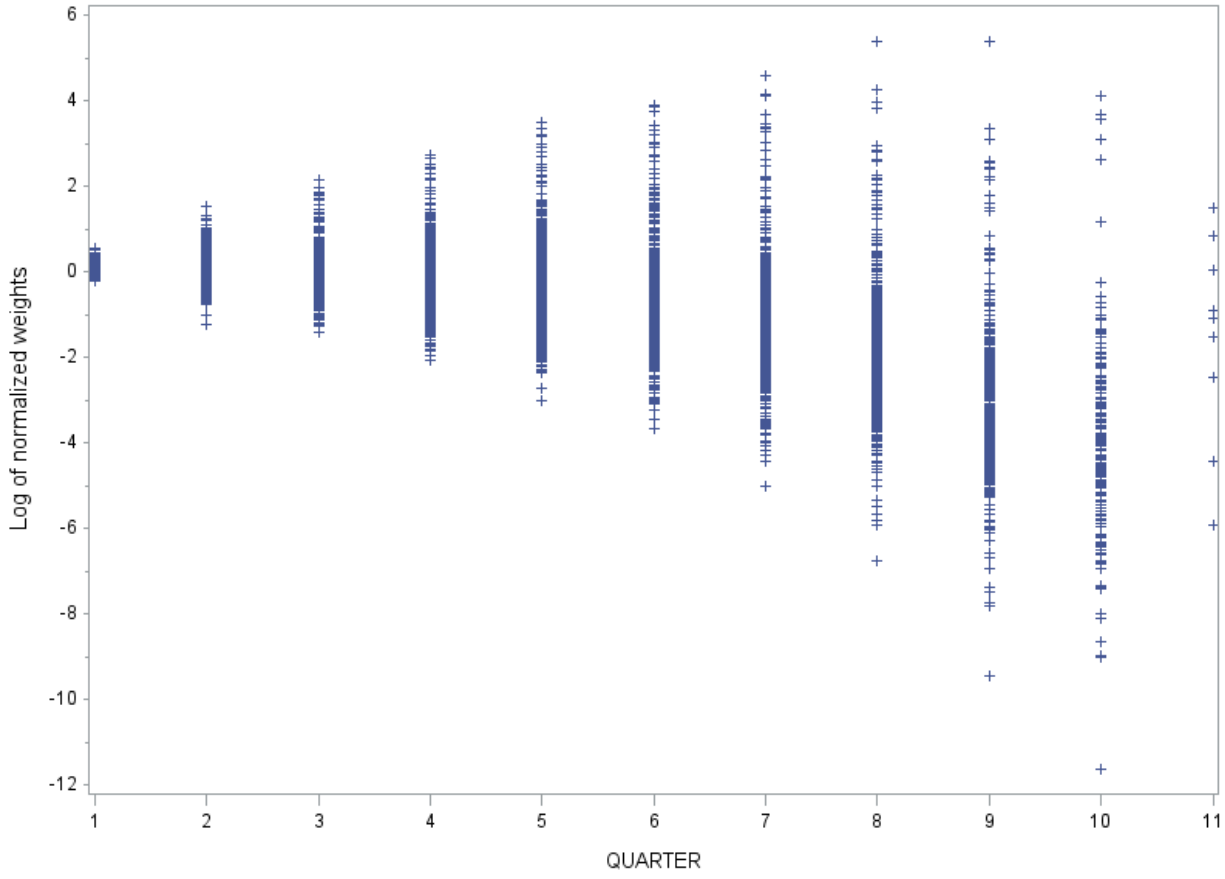

Figure X Log of normalized weights across quarters in cohort A (statin therapy)

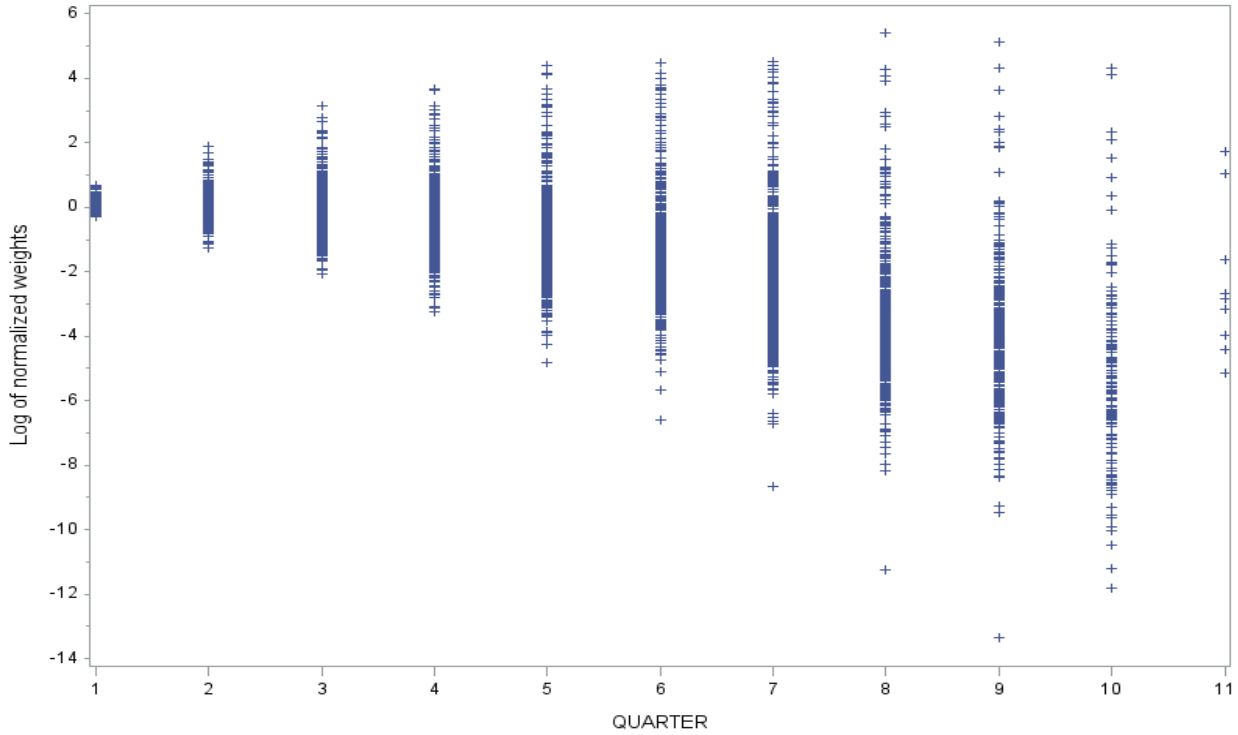

Figure XI Log of normalized weights across quarters in cohort B (β-blocker therapy)

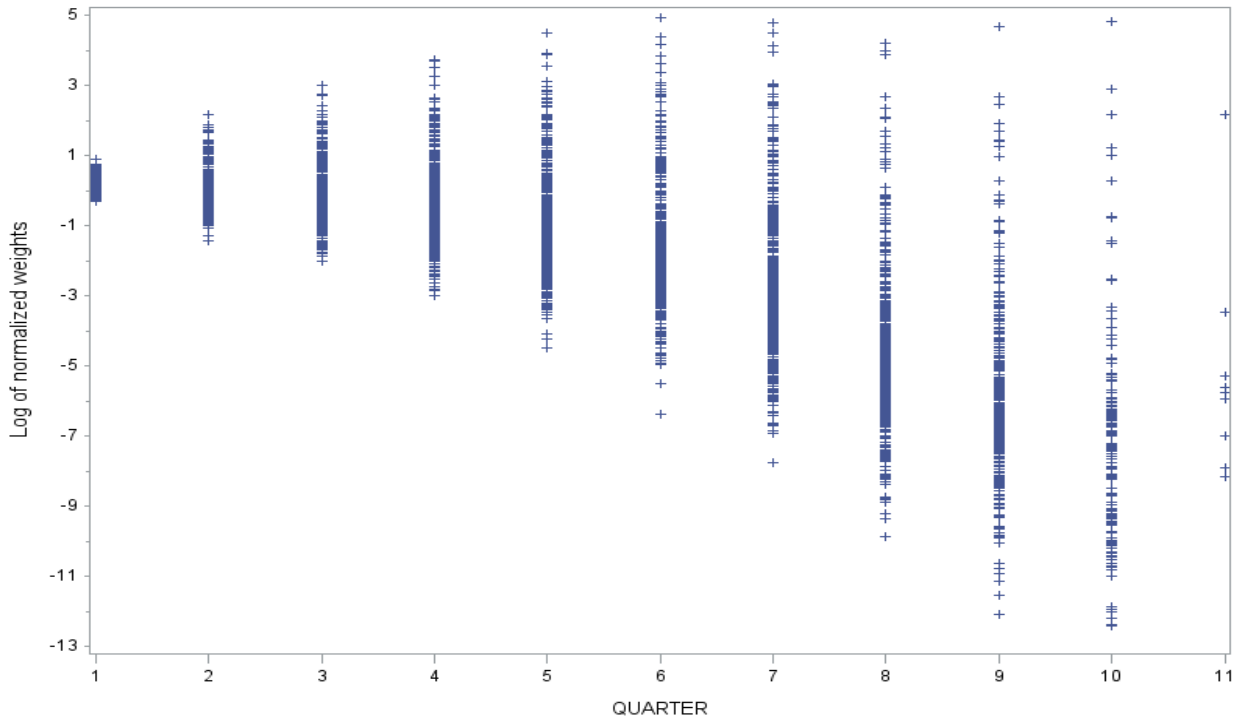

Figure XII Log of normalized weights across quarters in cohort C (ACEI/ARB therapy)

Table XXVIII Adjusted hazard ratios (HRs) from marginal structural models (MSMs) using normalized weights

	Cohort A (Statin Therapy) N = 1,091			Cohort B (β-blocker Therapy) N = 1,021			Cohort C (ACEI/ARB Therapy) N = 1,025		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
RECURRENT AMI									
Statin Adherence	0.60	[0.37, 0.95]	0.0312*						
β-blocker Adherence				1.07	[0.7, 1.59]	0.7388			
ACEI/ARB Adherence							1.09	[0.56, 2.15]	0.7960
MORTALITY									
Statin Adherence	0.95	[0.64, 1.39]	0.7789						
β-blocker Adherence				1.03	[0.68, 1.55]	0.8976			
ACEI/ARB Adherence							1.32	[0.78, 2.21]	0.2991

*$p<0.05$

HR, Hazards Ratio; AMI, acute myocardial infarction; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker

VITA

Tasneem T. Lokhandwala was born on the 28th of January 1986 in Mumbai, India. She is the daughter of Mr. Taher Lokhandwala and Mrs. Samina Lokhandwala.

She completed her Bachelor of Pharmaceutical Sciences at the University Institute of Chemical Technology (I.C.T), Mumbai, India in 2008. She completed her MS in Pharmaceutical Sciences with an emphasis in Pharmacy Administration from the University of Mississippi. She continued at the Department of Pharmacy Administration, University of Mississippi to complete her doctoral studies.

She is a member of Phi Kappa Phi, Rho Chi and the proud recipient of the Student Research Paper of the Year Award 2011-2012 and the William Farlow Fellowship 2010-2011.

At present she holds the position of Data Analyst, Global Health Economics and Outcomes Research at Xcenda ®, Palm Harbor, FL.