# Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers, Statins and Dementia in Patients with Heart Failure

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## PROJECT SUMMARY

Heart failure (HF) and dementia are common medical conditions in older adults.(1) More than 5.5 million adults have HF in the United States (US) and the incidence approaches 10 per 1000 population after 65 years of age. HF Heart failure (HF) is associated with increased risk of dementia and dementia that is a major growing public health problem in the United States and worldwide. One in six individuals older than 70 have dementia with prevalence increasing exponentially with advanced age. As a result, it is estimated that the number of dementia cases in 2050 will increase threefold compared with 2000. Dementia is an independent predictor of increased mortality in HF patients. There is increasing evidence that hypertension and dyslipidemia are associated with an increase in the risk of dementia, but it remains unclear whether anti-hypertensive and lipid-lowering agents alter the risk of dementia. **The goal of this study is to test whether angiotensin-converting enzyme inhibitors /angiotensin receptor blockers (ACEIs/ARBs) and statins alter the risk of dementia in patients with heart failure.** **Specific Aim 1** is to determine factors that predict treatment with ACEIs/ARBs and statins and to calculate propensity scores that will be used in Aim 3. **Specific Aim 2** is to test the association of ACEIs/ARBs and statins and time to dementia diagnosis in patients with heart failure using Cox hazards model. **Specific Aim 3** is to extend the analysis to marginal structural models and compare results from Aim 2 to estimates obtained from marginal structural models. We determined variation in incidence rates of dementia associated with socio-demographic factors (age, sex) and clinical factors (comorbid disease conditions and co-medications). We obtained propensity scores of treatments (ACEIs/ARBs and statins).To determine the unique effects of ACEIs/ARBs and statins after controlling for potential confounding factors, we adjusted for socio-demographic factors, comorbidities and co-medications in Cox hazards model of time to first diagnosis of dementia. Marginal structural

models using inverse probability of treatment weighting were used to test treatment effects, and results were compared to results obtained from Cox hazards regression. We conducted this study in a cohort of elderly with HF enrolled in a local Medicare Advantage Prescription Drug plan from 2008 to 2011. The study adds to the only outcomes, mortality and hospitalization considered in management of HF thus improving the quality of care. The findings from this observational study will help to address determinants of variation in treatment and our long range goal is to identify strategies to reduce the risk of dementia in this frail HF population.

## SPECIFIC AIMS

Heart failure and Dementia are common medical conditions in older adults.[1] More than 5.5 million adults have heart failure (HF) in the United States (US) and the incidence approaches 10 per 1000 population after 65 years of age.[2] Despite a decline in cardiovascular mortality in developed countries over the last three decades, the burden of heart failure (HF) has risen.[3, 4] Dementia is an independent predictor of increased mortality and of increased hospitalization in HF patients. [5-8] One in six individuals older than 70 has dementia with prevalence increasing exponentially with advanced age. It is estimated that the number of dementia cases in 2050 will increase threefold compared with the year 2000.[9] Alzheimer's Disease (AD) is the most common followed by vascular dementia (VaD) and other forms of dementia. There is considerable overlap emerging in the risk factors and pathogenesis of vascular dementia and Alzheimer's disease.[10]

HF is associated with more than an 80% increase in the risk of dementia and AD.[1, 11, 12] The probable biological pathways linking HF to dementia, and AD in particular, include considerably impaired cerebral circulation from HF, clinical and silent brain infarcts, leukoaraiosis, and cerebral thrombosis for which HF is a risk factor. A number of vascular comorbidities such as atrial fibrillation, hypertension, dyslipidemia and diabetes mellitus common in HF are linked to dementia.[13-17]. Another potential pathway is through the impaired cerebrovascular reactivity due to HF that could further aggravate hypoperfusion- related cerebral ischemia and neurodegeneration.[1, 16]

There is increasing evidence that hypertension and dyslipidemia are associated with an increase in the risk of dementia, but it remains unclear whether anti-hypertensive and lipid-lowering agents alter the risk of dementia.(18-21) **The goal of this study is to test whether**

**angiotensin-converting enzyme inhibitors /angiotensin receptor blockers (ACEIs/ARBs) and statins alter the risk of dementia in patients with heart failure.** The effects of ACEIs/ ARBs and statins upon the onset of dementia will be compared.

The study examines risk of dementia in HF as the health status outcome that is in line with the patient-centered care supported by Institute of Medicine to improve the quality of care in the US.[2] The study adds to the only outcomes, mortality and hospitalization considered in management of HF to improve quality of care. The findings from this observational study will help to address determinants of variation in treatment and comparative effectiveness of individual ACEIs, ARBs, and statins in complex patients at risk for dementia. This study will use state of the art methods to improve causal inference in non-randomized studies of comparative effectiveness of drug treatments.

**Specific Aim 1** is to determine factors that predict treatment with ACEIs/ARBs and statins. These factors were used to calculate propensity scores and were used for aim 3. Logistic regression was used to obtain propensity scores (predicted probability of receiving treatment with ACEIs/ ARBs and statins), based on (age, race/ethnicity, sex,) clinical factors (comorbid conditions) and treatment factors (co-medication use).

**Specific Aim 2** is to test the association of ACEIs/ARBs and statins with time to dementia using Cox hazards model. Cox hazards models of time to dementia diagnosis was constructed controlling for sociodemographic factors, comorbidities and co-medications.

We examined the effect of time varying exposure with outcome after adjustment for other time-dependent (hospitalization, low-density lipoprotein cholesterol-LDL-C test) and independent

(age, race/ethnicity, sex, comorbid conditions, co-medication use) confounding factors using extended/time dependent Cox hazards model.

Hypothesis 2.1: ACEIs/ARBs are associated with reduced risk of dementia after adjusting for demographic, clinical and treatment factors.

Hypothesis 2.2: Statins are associated with reduced risk of dementia after adjusting for demographic, clinical and treatment factors.

**Specific Aim 3** is to extend the analysis to marginal structural models and compare results from Aim 2 to estimates obtained from marginal structural models. Marginal structural models were used to test the unique effect of these drug treatments on time to diagnosis of dementia. These models employed inverse probability of treatment weighting (IPTW) to adjust for different propensity to receive treatments from Aim 1, with hospitalization and LDL-C as time-varying confounders affected by previous treatment.

Hypothesis 3.1: The estimates from MSMs will be different from the results obtained from time – dependent Cox model to test the association of ACEIs/ARBs with time to dementia diagnosis.

Hypothesis 3.2: The estimates from MSMs will be different from the results obtained from time-dependent Cox model to test the association of statins with time to dementia diagnosis.

## BACKGROUND, SIGNIFICANCE AND RATIONALE

Heart failure and Dementia are common medical conditions in older adults.[1] More than 5.5 million adults have heart failure (HF) in the United States (US) and the incidence approaches 10 per 1000 population after 65 years of age.[2] Despite a decline in cardiovascular mortality in developed countries over the last three decades, the burden of heart failure (HF) has risen.[3, 4] Dementia is an independent predictor of increased mortality and of increased hospitalization in HF patients. [5-8] One in six individuals older than 70 have dementia with prevalence increasing exponentially with advanced age. It is estimated that the number of dementia cases in 2050 will increase threefold compared with the year 2000.[9] Alzheimer's Disease (AD) is the most common followed by vascular dementia (VaD) and other forms of dementia. There is considerable overlap emerging in the risk factors and pathogenesis of vascular dementia and Alzheimer's disease.[10]

HF is associated with more than an 80% increase in the risk of dementia and AD.[1, 11, 12] The probable biological pathways linking HF to dementia, and AD in particular, include considerably impaired cerebral circulation from HF, clinical and silent brain infarcts, leukoaraiosis, and cerebral thrombosis for which HF is a risk factor. A number of vascular comorbidities such as atrial fibrillation, hypertension, dyslipidemia and diabetes mellitus common in HF are linked to dementia.[13-17]. Another potential pathway is through the impaired cerebrovascular reactivity due to HF that could further aggravate hypoperfusion-related cerebral ischemia and neurodegeneration.[1, 16] It is important to note that "vascular risk factors" appear to increase the risk of AD through non-vascular mechanisms. So, while all of the vascular mediated mechanisms listed are plausible and possible, it is thought that other non-vascular mechanisms are probably the link between these risk factors and AD.

Numerous studies have found that hypertension is a risk factor for dementia.[18-20] Therefore, its control in HF patients should be beneficial in reducing the incidence of dementia.[21] Our previous work showed that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were better than other anti-hypertensive agents in reducing the risk of dementia in elderly diabetic patients. There are plausible biological rationales to support the protective effects of ACEIs/ARBs in dementia. Recent findings support that the brain has its own renin–angiotensin system, and ACEI/ARB may regulate it to show neuroprotection. ACEIs/ARBs have been shown to restore normal cerebral autoregulation, reverse inflammatory reactions, decrease neuronal cell death, and have antiplatelet aggregating and atrial antifibrillatory effects. [22-24] However, there are studies that found no association with use of ACEIs/ARBs and risk of dementia.[25, 26] To our knowledge there is no study in HF patients that assessed the effect of ACEIs/ARBs on time to dementia diagnosis. Moreover, literature showed that ACEIs/ARBs have different effect on cognitive impairment in patients with and without HF[27] and dementia significantly increased the risk of hospitalization and mortality in HF patients.[5, 7, 8] Given the significant clinical impact of dementia associated with HF and the current urgency for effective treatments to reduce the incidence of dementia, the present study examines the effectiveness of ACEI/ARB that are widely prescribed for the treatment of HF.

There is increasing evidence that dyslipidemia may be involved in the pathogenesis of dementia (AD and VaD).[28-36] Therefore, statins, a class of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [37, 38] might reduce the risk of dementia by lowering cholesterol. Statins have been shown to have an inhibiting effect on β-amyloid that triggers progression to Alzheimer's disease.[39, 40] Besides lipid lowering ability, statins also have pleiotrophic effects. These include endothelial protection by increasing nitric oxide, as well as

antioxidant, anti-inflammatory, and antithrombotic effects. [35, 41] They may also reduce cellular death. [42] These effects implicate the ability of statins to act via cholesterol independent signaling pathways.[43] However, there is a mixed body of evidence as to whether statins reduce the risk of dementia.[44-46] Some evidence suggests a favorable effect of statins on cognition[47-50] while other studies have failed to show beneficial effects on cognitive function.[51-55]

Many non-randomized studies have suggested benefits of statins in patients with HF and a number of prospective studies in ischemic and nonischemic HF have shown favorable effects on left ventricular function and clinical status.[56-62] Recently the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)[63] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca (GISSI) trials[64] demonstrated that statins are safe in patients with heart failure. The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of HF 2008 suggests consideration of the use of statins in elderly patients with symptomatic chronic HF and systolic dysfunction caused by coronary artery disease to reduce cardiovascular hospitalization.[65, 66]The American College of Cardiology (ACC) Foundation/American Heart Association(AHA) task force on practice guidelines 2009 recommend use of diuretic, an ACEI or an ARB, and a beta blocker for routine management of HF.[67]

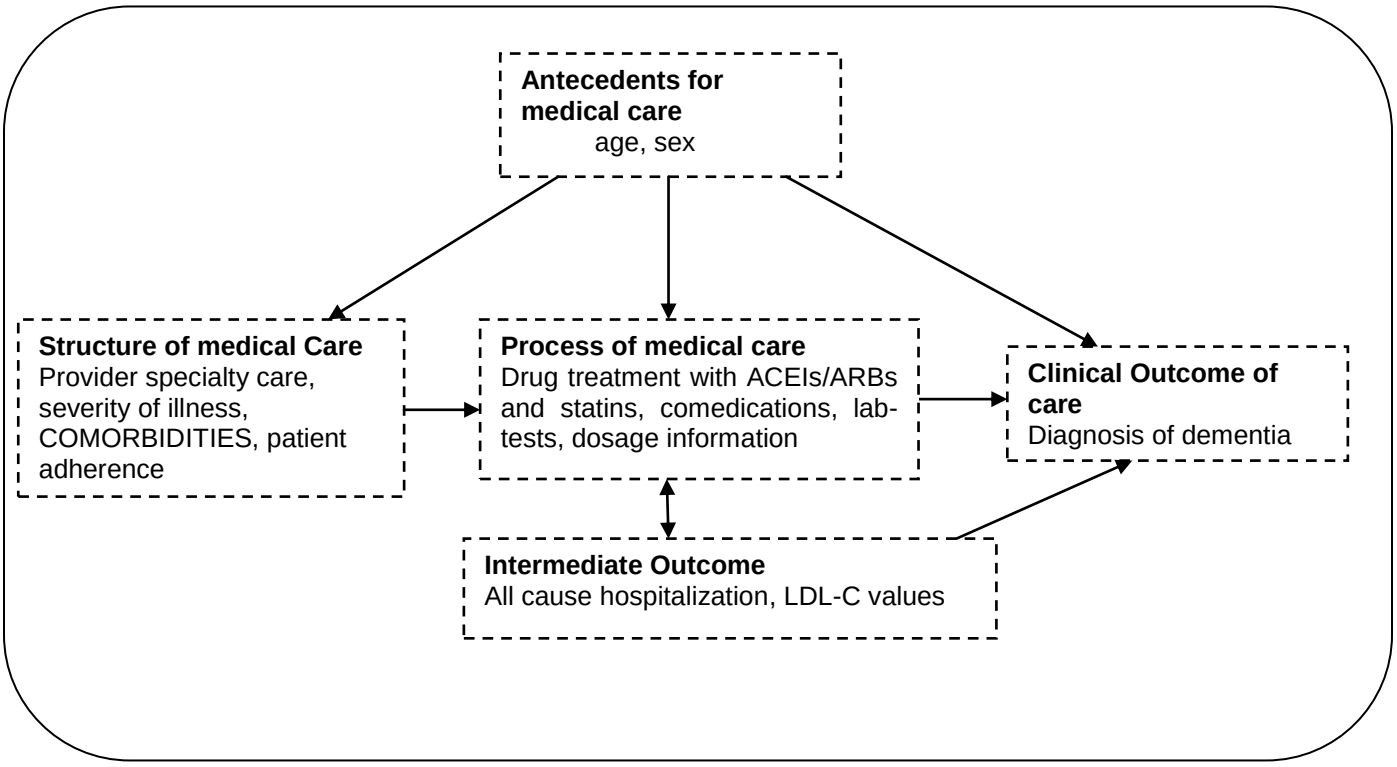
Therefore the purpose of this observational study is to test **whether ACEIs/ARBs and Statins reduce the risk of dementia in patients with heart failure.**

The following conceptual framework by Coyle and Battles (1999) will guide the work in the study.[68] Coyle and Battles (1999) modified the Donabedian model to include important antecedent conditions in addition to the paradigm of structure, process, and outcome to

evaluate quality of care.[69] The framework assesses the effects of antecedent, structural, medical care process variables on outcomes of care.

The antecedent factors in the study will include individual's personal characteristics like socio-demographics (age, sex). The elements in structure of care will include provider characteristics like specialty of provider and patient characteristics like severity of illness, comorbidities, patient adherence to treatment. The process of care will include medication prescribed and tests ordered. The outcomes are the ultimate tests of effectiveness of medical care. The current study will extend the framework by Coyle and Battles to include intermediate outcomes as hospitalization and low-density lipoprotein-cholesterol (LDL-C) lab values which in turn affects the process of care elements. The main clinical outcome in the study is the diagnosis of dementia as depicted in the schematic below.

**CONCEPTUAL FRAMEWORK FOR STUDY**



**Significance and Innovation**

There are no studies to date that have examined the effect of the ACEI/ARBs and Statins on risk of dementia in HF patients. The findings from this exploratory study will add to the empirical knowledge of effect of these drugs and to reduce the risk of dementia. The use of marginal structural models is relatively new and innovative in HF reasearch.

**What does the study add?**

- The study builds upon the prior work done by Mr. Chitnis in HF and use of individual ACEIs.[70, 71]
- It uses marginal structural models using IPTW which is a step further to the innovative method used by Mr. Chitnis in his Master's thesis.[70, 71]
- The study advances the work done by Dr. Johnson and his team further in the HF domain and dementia.[18-20, 72-75]
- The study uses some important clinical factors like the creatinine, HbA1c and LDL-C values that were not recorded in the previous work.
- The study fills in the gaps in the prior work
    - Uses marginal structural models that reduce or eliminate the bias due to confounding by time varying covariates and exposure. The prior work on risk to dementia used Cox proportional analysis with only time independent covariates and exposure.
    - Extends the follow up to a 3 year period. The prior work used follow up to a 2 year period

  - Employs a new user design for drug exposure to improve interpretation of results in subgroup analysis. The prior work examined the period prevalence of drug exposure.
  - Applies to general HF population from Medicare Advantage plan. The prior studies included concern that the VA population was not representative of the general population as they are mostly male and may differ with respect to other socio-demographic factors.

- The study uses dose information of the ACEIs/ARBs and statins as time –varying factors to strengthen the results as dose plays an important role in predicting the clinical outcomes in HF patients
- The study adds to the empirical knowledge of use of these drugs in HF as there are no studies till date that have examined the effect of the ACEI/ARBs and statins on risk of dementia in HF patients.

## Study design details, results, conclusions in the form of manuscripts drafts

Manuscript 1- Specific Aim 1

Manuscript 2- Specific Aim 2.1 & Specific Aim 3.1

Manuscript 3- Specific Aim 3.1 & Specific Aim 3.2

# MANUSCRIPT 1

## Predictors of angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers and statins in heart failure


### Abstract

**Objective:** The aim of this study was to identify the factors associated with use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEIs/ARBs) and statins in patients with heart failure (HF).

**Methods:** This retrospective, longitudinal study used a cohort of patients with HF identified from a local Medicare advantage prescription drug plan to examine the factors associated with the use of ACEIs/ARBs and statins within one year of follow-up from 2009 through 2010. Multiple logistic regressions were used in the conceptual framework of the quality of care to examine the factors associated with use of ACEIs/ARBs and statins.

**Results:** A total of 6845 HF patients with a mean age 74.50 ±9.18 years were identified. About 50% received ACEIs/ARBs and 44% received statins within one year of follow up period. Most of the patients had hypertension (87.04%) followed by hyperlipidemia (59.30%), ischemic heart disease (48.04%), diabetes (45.13%) and chronic lung disease (37.52%). Being male, of older age, having vavular heart disease, chronic lung disease, anemia and coagulation disorder, thyroid disorder, other psychiatric disorder, higher CMS score and vasodilator use had decreased odds of receiving ACEIs/ARBs. Hypertension, greater number of years with heart failure and hypoglycemic use was associated with increased likelihood of receiving ACEI/ARB. Similarly, age, years with heart failure, comedications, comorbidities and prior hospitalization were significantly predicted the use of statins.

**Conclusions:** Nearly half of the HF patients received ACEIs/ARBs and statins. In addition to hypertension and hyperlipidemia other factors like age, years with heart failure, use of other medications and comorbidities played an important role in predicting the use of ACEIs/ARBs and statins.

## Introduction

Heart failure (HF) is a complex clinical syndrome that can result from any structural or functional cardiac disorder that impairs the ability of the ventricle to fill with or eject blood. The cardinal manifestations of HF are

1. dyspnea and
2. fatigue,

These conditions may limit exercise tolerance, and fluid retention, which may lead to pulmonary congestion and peripheral edema. Both abnormalities can impair the functional capacity and quality of life of affected individuals, but they do not necessarily control the clinical picture at the same time. A few patients have exercise intolerance but little evidence of fluid retention, whereas others have edema and some indication of dyspnea or fatigue.[67]

**Incidence**

Data from the National Heart, Lung, and Blood Institute (NHLBI)- indicate that:

— HF incidence approaches 10 per 1000 population after 65 years of age.

— Seventy-five percent of HF cases have antecedent hypertension.

— At 40 years of age, the lifetime risk of developing HF for both men and women is 1 in 5. At 80 years of age, remaining lifetime risk for development of new HF remains at 20% for men and women, even in the face of a much shorter life expectancy.

— At 40 years of age, the lifetime risk of HF occurring without antecedent MI is 1 in 9 for men and 1 in 6 for women.

— The lifetime risk for people with BP >160/90 mm Hg is double that of those with BP <140/90 mm Hg.[76]

**Mortality**

In 2005, HF total-mention mortality was 292 214. HF was mentioned on 292 214 US death certificates and was selected as the “underlying cause” in 58 933 of those deaths (National Center for Health Statistics). In preliminary 2006 mortality, HF was selected as the “underlying cause” in 60 315 deaths. Unlike other cardiovascular diseases, HF is the end stage of a cardiac disease. It is mostly a consequence of hypertension, coronary heart disease (CHD), valve deformity, diabetes, or cardiomyopathy. The other causes of heart failure are relatively less. For each of the 58 933 deaths, the true underlying cause—ie, the “etiology” of HF—is not known. The number of HF deaths has increased steadily despite advances in treatment, in part because of increasing numbers of patients with HF due to better treatment and “salvage” of patients with acute myocardial infarctions (MIs) earlier in life.[77]

**Hospitalisation**

From 1990 to 1999, the annual number of hospitalizations has increased from approximately 810 000 to over 1 million for HF as a primary diagnosis and from 2.4 to 3.6 million for HF as a primary or secondary diagnosis.[78] The hospital discharges in 2006 was 1 106 000. [76]

**Cost**

The estimated direct and indirect cost of HF in the United States for 2009 is $37.2 billion.[76]

**Statins and angiotensin-converting enzyme inhibitor/angiotensin recetor blockers(ACEIs/ARBs) in HF**

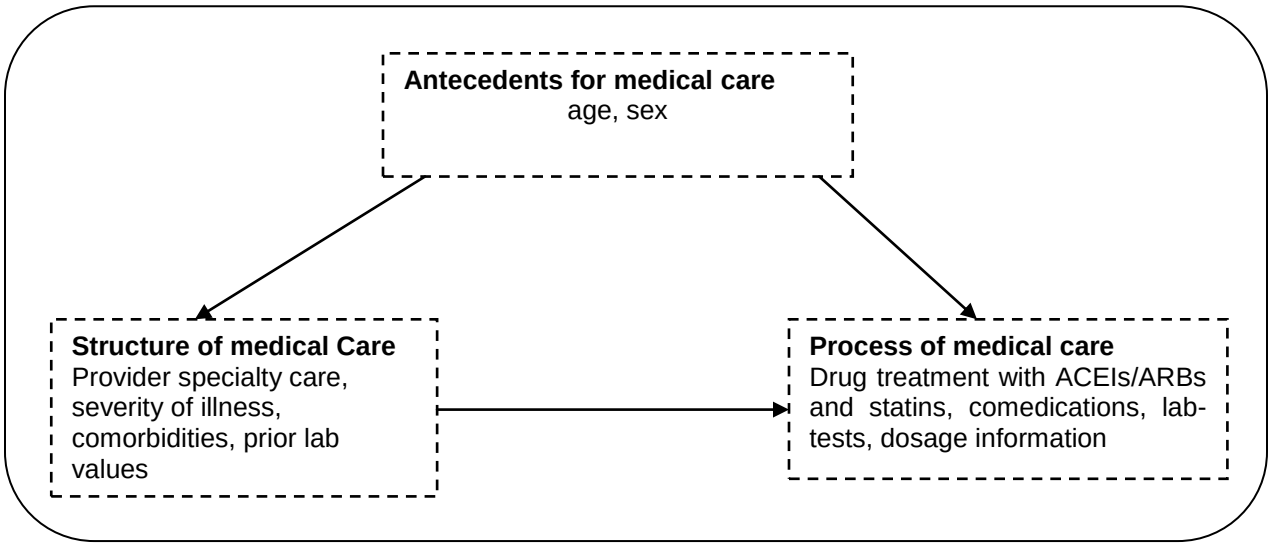
Many non-randomized studies have suggested benefits of statins in patients with HF and a number of prospective studies in ischemic and nonischemic HF have shown favorable effects on left ventricular function and clinical status.[56-63] Recently the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)[63] and the Gruppo Italiano per lo Studio della Sopravvivenza nell’Insufficienza cardiaca (GISSI) trials[64] demonstrated that statins are safe in patients with heart failure. The European Society of Cardiology (ESC) guidelines for the

diagnosis and treatment of HF 2008 suggests consideration of the use of statins in elderly patients with symptomatic chronic HF and systolic dysfunction caused by coronary artery disease to reduce cardiovascular hospitalization.[65] The American College of Cardiology (ACC) Foundation/American Heart Association(AHA) task force on practice guidelines 2009 recommend use of diuretic, an ACEI or an ARB, and a beta blocker for routine management of HF.[67]

The following conceptual framework by Coyle and Battles (1999) will guide the work in the study.[68] Coyle and Battles (1999) modified the Donabedian model to include important antecedent conditions in addition to the paradigm of structure, process, and outcome to evaluate quality of care.[69] The framework assesses the effects of antecedent, structural medical care variables on process and outcomes of care. In this study our aim to determine the predictors associated with the process of care i.e. use of ACEI/ARBs and statins.

The antecedent factors in the study will include individual's personal characteristics like socio-demographics (age, sex). The elements in structure of care will include provider characteristics and patient characteristics like severity of illness, comorbidities. The process of care will include medication prescribed and tests ordered as depicted in the schematic below.

**CONCEPTUAL FRAMEWORK FOR STUDY**




Though there is substantial evidence for the treatment of HF, there is almost no evidence regarding the factors that predict the use of ACEI/ARBs and statins in this frail population. The long range goal of this study is to improve the care of elderly with HF. Therefore, the aim of the study is to determine the factors which decide on the prescription of ACEI/ARB and statins in patients with HF.

## Methods

*Data source*

The study design was a retrospective longitudinal cohort of all HF patients in a Medicare Advantage Prescription Drug (MAPD) plan in Texas from January 1, 2008, to December 31, 2010. Several computerized data files including membership file, member summary file, institutional claims file, professional claims file, quest lab, CCMS and pharmacy file were used. Membership and member summary files include demographic, severity scores and cost data for beneficiaries for each year. Institutional claims include information on all inpatient claims. The files contain diagnostic information in the form of International Classification of Diseases, Ninth Revision (ICD-9) codes, and procedure information in form of Current Procedural Terminology

(CPT) codes. Professional claims contain information on all outpatient encounters. The files contain diagnostic information in the form of ICD-9-CM codes and procedure information in form of CPT codes. Quest lab files contain 153 applicable lab tests that include low-density lipoprotein (LDL-C), hemoglobin A1c (HbA1c) and creatinine. CCMS file include the hospitalization records, date of admission, date of discharge and length of stay. Pharmacy files contain Part D pharmacy data provided by pharmacy benefits manager. The pharmacy records include patient and drug identifying information, fill dates, days of supply, quantity dispensed and dosing information for each prescription filled.

*Selection of patients*

Patients were included in the study sample if they had at least one claim after the index date and diagnosed with HF (ICD-9-CM 402.01, 402.11, 402.91, 415.0X, 416.9X, 425.4X-425.9X, 428.XX, 429.4X, 785.51) between January 1, 2008, to December 31, 2011. Patients were excluded if they were diagnosed with dementia or died before the index date. Index date was defined as January 1, 2009 for patients that had HF diagnosis on or before January 1, 2009 and their coverage prior to January 1, 2008; date of HF diagnosis for patients that had 1 or more years of records prior to HF diagnosis or date at which the HF patients had at least 1 year prior records. Finally, records with missing values except for the laboratory measures were deleted from the final sample, as suggested by Little and Rubin (1989).[79]

Outcome measure

A patient's use of ACEI/ARB statins was assessed for one year after the index date during the study period (01/01/2009 -12/31/2011).

Predictors

The variation in use of ACEIs/ARBs may be associated with socio-demographic factors, treatment factors and clinical factors, therefore the study included 43 such covariates. Socio-demographic factors included age and gender. Treatment factors included various co-medications taken 1 year prior to the index date. We included diuretics (thiazide diuretics, potassium sparing diuretics and loop diuretics), digitalis glycosides, calcium channel blockers (CCBs), beta blockers (BBs), vasodilators, anti arrythmics, alpha blockers, insulin, oral hypoglycemics and non statin lipotropics. Clinical factors included 22 co-morbid conditions [70, 71, 80, 81] and appropriate laboratory measures like serum creatinine, low-density lipoprotein (LDL-C), hemoglobin A1c (HbA1c). Severity of illness could not be assessed by ejection fraction (EF) or New York Heart Association (NYHA) HF classification due to lack of information in the database. Instead we used number of years in the cohort and prior hospitalization as a substitute for HF severity[70, 71]. We also included number of all drugs taken, number of co-morbid conditions and Centers for Medicare and Medicaid Services (CMS) risk score to account for medication burden and disease severity. The CMS risk score is calculated based on data taken from a large pool of beneficiaries to estimate the average predicted costs for each of the component factors (e.g., age-sex, low income status, individual disease groups). It consists of 189 disease classifications for use in risk adjusting of clinical outcomes in Medicare populations.[18, 19]

*Statistical analysis*

Analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC). Bivariate associations between the predictor variables and outcomes were tested using the chi-square test for categorical variables and the t test for continuous variables. Multivariable logistic regressions were used to test the factors associated with use of ACEI/ARB and statin. A *P* value of 0.05 was considered to be statistically significant.

## Results

Thus, the study sample comprised 6845 HF patients that had at least one year of follow up between January 01, 2009 and December 31, 2010. The mean age of the cohort was 74.50 ±9.18 years and had 47.36% males and 52.64% females. About 54.20% patients were taking more than 3 medicines and diuretics (63.64%) was highest prescribed followed by betablockers (56.14%), calcium channel blockers (33.02%), hypoglycemic drugs (30.49%) and vasodilators(19.47%). Of the 21 co-morbid conditions, top five co-morbid conditions were hypertension (87.04%), hyperlipidemia (59.30%), ischemic heart disease (48.04%), diabetes (45.13%) chronic lung disease (37.52%).A higher percentage (41.39%) of patients were incident cases for HF as compared to 22.67%, 17.01%, 18.93% of patients who had HF for 1 year, 2 years, and 3 years respectively.42.10% patients had hospitalization in prior years. The HF patient characteristics are demonstrated in Table 1.

**Table 1. CHF patient characteristics**

| | Frequency | Percentage |
|---|---|---|
| **Patient count** | 6845 | 100 |
| **Age** mean(SD) | 74.5 | 9.1 |
| **Age groups** | | |
| < 65 | 776 | 11.34 |
| 65-74 | 2659 | 38.85 |
| 75-84 | 2621 | 38.29 |
| >=85 | 789 | 11.53 |
| **Gender** | | |
| Males | 3242 | 52.64 |
| Females | 3603 | 47.36 |
| **CMS Risk Scores** mean (SD) | 1.64 | 1.15 |
| **Co-morbidities** | | |
| Hypertension | 5958 | 87.04 |
| Ischemic Heart Disease | 3288 | 48.04 |
| Conduction Disorders | 1124 | 16.42 |
| Cardiac Arrhythmias | 1689 | 24.67 |
| Valvular Heart Disease | 1571 | 22.95 |
| Cerebrovascular Disease | 1105 | 16.14 |
| Chronic lung disease | 2568 | 37.52 |
| Diabetes | 3643 | 45.19 |
| Renal disease/Renal Failure | 1871 | 27.33 |

| | Frequency | Percentage |
|---|---|---|
| Disorders of upper GI and Liver | 592 | 8.65 |
| Non-Skin Malignancies | 697 | 10.18 |
| Anemia & Coagulation Disorders | 1511 | 22.07 |
| Decubitus and LE ulcers | 367 | 5.36 |
| Thyroid Disorders | 1145 | 16.73 |
| Sleep Apnea | 327 | 4.78 |
| Alcohol Related Disease | 65 | 0.95 |
| Other Psychiatric Disorders | 1068 | 15.60 |
| Pulmonary Heart Disease | 386 | 5.64 |
| Thromboembolism | 395 | 5.77 |
| Hyperlipidemia | 4059 | 59.30 |
| Peripheral arterial disease | 1485 | 21.69 |
| **Prior hospitalization** | 2882 | 42.10 |
| **Number of co-morbid conditions** | | |
| Less than or equal to 5 | 4176 | 61.01 |
| More than 5 | 2669 | 38.99 |
| **Years with HF** | | |
| 0 | 2833 | 41.39 |
| 1 | 1552 | 22.67 |
| 2 | 1164 | 17.01 |
| =>3 | 1296 | 18.93 |
| **Co-medications** | | |
| Beta Blocker Use | 3843 | 56.14 |
| CCB Use | 2260 | 33.02 |
| Digoxin Use | 751 | 10.97 |
| Vasodilators Use | 1333 | 19.47 |
| Diuretics Use | 4356 | 63.64 |
| Alpha blockers use | 329 | 4.81 |
| Anti Arrythmic use | 360 | 5.26 |
| Insulin use | 978 | 14.29 |
| Hypoglycemic use | 2087 | 30.49 |
| Non- statin lipotropic use | 1059 | 15.47 |
| ACEIs/ARBs use ( within 1 year) | 3438 | 50.22 |
| Statins use (within 1 year) | 3023 | 44.16 |
| **Number of drugs** | | |
| Less than or equal to 3 | 3135 | 45.80 |
| More than 3 | 3710 | 54.20 |
| **Serum creatinine level** | | |
| <1.5 | 3734 | 54.55 |
| 1.5-2.5 | 630 | 9.20 |
| >2.5 | 151 | 2.21 |
| Unknown | 2330 | 34.04 |
| **Low-density lipoprotein** | | |
| <100 | 2271 | 33.18 |

| | Frequency | Percentage |
|---|---|---|
| 100-129 | 901 | 13.16 |
| >129 | 543 | 7.93 |
| Unknown | 3130 | 45.73 |
| **HbA1c** | | |
| <7 | 1543 | 22.54 |
| >7 | 715 | 10.45 |
| Unknown | 4587 | 67.01 |

**Table 2. Factors that significantly predict the use of ACEIs/ARBs**

| Effect | | OR | 95% CI | | P value |
|---|---|---|---|---|---|
| Sex | M vs F | 0.832 | 0.745 | 0.930 | 0.0012* |
| Age | 65-74 vs < 65 | 0.846 | 0.711 | 1.006 | 0.0591 |
| | 75-84 vs < 65 | 0.712 | 0.595 | 0.851 | 0.0002* |
| | >=85 vs < 65 | 0.538 | 0.430 | 0.674 | <.0001* |
| Years with HF | 1 vs 0 | 1.603 | 1.401 | 1.835 | <.0001* |
| | 2 vs 0 | 1.862 | 1.595 | 2.173 | <.0001* |
| | 3 or more vs 0 | 2.112 | 1.819 | 2.451 | <.0001* |
| Co-medications | Vasodilators use | 0.835 | 0.725 | 0.961 | 0.012* |
| | Hypoglycemic use | 1.189 | 1.014 | 1.393 | 0.0338 |
| Co-morbidities | Hypertension | 1.932 | 1.635 | 2.282 | <.0001* |
| | Valvular Heart Disease | 0.840 | 0.736 | 0.959 | 0.010* |
| | Chronic lung disease | 0.746 | 0.665 | 0.836 | <.0001 |
| | Anemia & Coagulation Disorders | 0.807 | 0.704 | 0.924 | 0.002* |
| | Decubitus and LE ulcers | 0.697 | 0.548 | 0.886 | 0.003* |
| | Thyroid Disorders | 0.842 | 0.731 | 0.969 | 0.017* |
| | Other Psychiatric Disorders | 0.803 | 0.694 | 0.929 | 0.003* |
| CMSRiskScore | | 0.877 | 0.832 | 0.925 | <.0001* |
| Number of drugs | >3 vs <=3 | 1.915 | 1.617 | 2.269 | <.0001* |
| Serum creatinine level | 1.5-2.5 vs <1.5 | 0.962 | 0.794 | 1.166 | 0.695 |
| | >2.5 vs <1.5 | 0.388 | 0.266 | 0.567 | <.0001* |
| | Unknown vs <1.5 | 0.906 | 0.764 | 1.074 | 0.256 |

* indicates statistically significant values

1. Sex- As compared to the females, males are 16.8% less likely to receive ACEIs/ARBs.
2. Age- As age increases, the chances of getting ACEIs/ARBs decrease.

   The odds of receiving ACEIs/ARBs are 28.8% less for patients aged between 75 and 84 as compared with patients less than 65 years of age

The odds of receiving ACEIs/ARBs are 46.2% less for patients aged above 85 years as compared with patients less than 65 years of age

3. Years with heart failure- As years with HF increase, the chances of getting ACEIs/ARBs increase.

   Patients with 1 year of HF are 1.6 times likely to receive ACEIs/ARBs as compared with new HF cases.

   Patients with 2 years of HF are 1.9 times likely to receive ACEIs/ARBs as compared with new HF cases.

   Patients with 3 or more years of HF are 2.1 times likely to receive ACEIs/ARBs as compared with new HF cases.

4. Co-medications used

   The odds of receiving ACEIs/ARBs are 16.5% less for patients using vasodilators.

   The odds of receiving ACEIs/ARBs are 18.9% higher for patients using oral hypoglycemics.

5. Co-morbidities

   Patients with hypertension are 1.9 times more likely to receive ACEIs/ARBs.

   Patients with valvular heart disease are 16% less likely to receive ACEIs/ARBs.

   Patients with chronic lung disease are 25.4% less likely to receive ACEIs/ARBs.

   Patients with anemia & coagulation disorders are 19.3% less likely to receive ACEIs/ARBs.

   Patients with decubitus and LE ulcers are 30.3% less likely to receive ACEIs/ARBs.

   Patients with thyroid disorders are 15.8% less likely to receive ACEIs/ARBs.

   Patients with other psychiatric disorders are 19.7% less likely to receive ACEIs/ARBs.

6. CMS risk score- One unit increase in CMS risk score is associated with 12.3% decrease in odds of receiving ACEIs/ARBs.
7. Number of Drugs - Patients taking 3 or more drugs have 91.5% increase in odds of receiving ACEIs/ARBs.

**Table 3. Factors that significantly predict the use of Statins**

| Effect | | OR | 95% CI | | P value |
|---|---|---|---|---|---|
| Age | 65-74 vs < 65 | 1.045 | 0.876 | 1.246 | 0.6275 |
| | 75-84 vs < 65 | 0.864 | 0.720 | 1.036 | 0.1145 |
| | >=85 vs < 65 | 0.611 | 0.483 | 0.772 | <.0001* |
| Years with HF | 1 vs 0 | 1.422 | 1.237 | 1.633 | <.0001* |
| | 2 vs 0 | 1.649 | 1.408 | 1.930 | <.0001* |
| | 3 or more vs 0 | 1.691 | 1.452 | 1.969 | <.0001* |
| Co-medications | Diuretics use | 0.835 | 0.735 | 0.950 | 0.006* |
| | Digoxin use | 1.189 | 1.014 | 1.393 | 0.0002* |
| Co-morbidities | Ischemic Heart Disease | 1.371 | 1.211 | 1.553 | <.0001* |
| | Cardiac Arrhythmias | 0.841 | 0.729 | 0.971 | 0.018* |
| | Cerebrovascular Disease | 1.184 | 1.019 | 1.375 | 0.027* |
| | Chronic lung disease | 0.880 | 0.782 | 0.990 | 0.034* |
| | Anemia & Coagulation Disorders | 0.833 | 0.724 | 0.959 | 0.011* |
| | Decubitus and LE ulcers | 0.734 | 0.572 | 0.941 | 0.015* |
| | Sleep Apnea | 1.397 | 1.091 | 1.788 | 0.008* |
| | Alcohol Related Disease | 0.479 | 0.260 | 0.880 | 0.018* |
| | Hyperlipidemia | 1.996 | 1.773 | 2.247 | <.0001* |
| Prior hospitalization | | 0.865 | 0.761 | 0.983 | 0.026* |
| Number of drugs | >3 vs <=3 | 2.424 | 2.038 | 2.883 | <.0001* |
| Serum creatinine level | 1.5-2.5 vs <1.5 | 0.940 | 0.773 | 1.144 | 0.538 |
| | >2.5 vs <1.5 | 0.464 | 0.316 | 0.681 | <.0001* |
| Low-density lipoprotein | >129 vs <100 | 0.776 | 0.634 | 0.950 | 0.0142* |

* indicates statistically significant values

1. Age- As age increases, the chances of getting statins decrease.

   The odds of receiving statins are 38.9% less for patients aged above 85 years as compared with patients less than 65 years of age
2. Years with heart failure- As years with HF increase, the chances of getting statins increase.

   Patients with 1 year of HF are 1.4 times likely to receive statins as compared with new HF cases.

Patients with 2 years of HF are 1.6 times likely to receive statins as compared with new HF cases.

Patients with 3 or more years of HF are 1.7 times likely to receive statins as compared with new HF cases.

3. Co-medications used

   The odds of receiving statins are 16.5% less for patients using diuretics.

   The odds of receiving statins are 18.9% more for patients using digoxin.

4. Co-morbidities

   Patients with ischemic heart disease are 1.3 times more likely to receive statins.

   Patients with cardiac arrhythmias are 15.1% less likely to receive statins.

   Patients with cerebrovascular disease are 1.2 times more likely to receive statins.

   Patients with chronic lung disease are 12% less likely to receive statins.

   Patients with anemia & coagulation disorders are 16.7% less likely to receive statins.

   Patients with decubitus and LE ulcers are 27.5% less likely to receive statins.

   Patients with sleep apnea are 39.7% more likely to receive statins.

   Patients with alcohol related disease are 52.1% less likely to receive statins.

   Patients with hyperlipidemia are 2 times more likely to receive statins.

5. Prior hospitalization- Patients that had prior hospitalization had 13.5% less odds of receiving statins.
6. Numbers of Drugs - Patients taking 3 or more drugs are 2.4 times more likely of receiving statins.

## Discussion

The aim of this study was to find out the predictors of ACEI/ARBs and statins use in the HF population. To our knowledge, there are no studies till date to determine the predictors of

ACEIs/ARBs and statins use in elderly HF patients. As expected, hypertension and hyperlipidemia were found out to be the most important predictors of ACEI/ARB and statin use respectively. Patients with hypertension were 1.9 times more likely to receive ACEIs/ARBs while patients with hyperlipidemia were 2 times more likely to receive statins. These findings were consistent with literature showing the reduced risk of heart conditions by use of ACEIs/ARBs and statins [82-86] There were some interesting facts that were noticed from the findings of this study like patients suffering from chronic lung disease, anemia & coagulation disorders had less chance of receiving both ACEIs/ARBs and statins. Also, as the age increased the chances of receiving ACEIs/ARBs and statins decreased, whereas as the number of years with CHF increased the likelihood of receiving ACEIs/ARBs and statins increased. One of the reasons for decreased use of these medications with age could be that as the patient ages she may become weaker and the capacity of the patient to tolerate the medications decreases at the same time as the years with heart failure progresses these medications may be required to restore the functioning of the failing heart.

## Conclusion

This exploratory study found that nearly half of the HF patients received ACEIs/ARBs and statins. In addition to hypertension and hyperlipidemia other factors like age, years with heart failure, use of other medications and comorbidities played an important role in predicting the use of ACEIs/ARBs and statins.

# MANUSCRIPT 2

## Use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and risk of dementia in heart failure

**Abstract**

**Objective:** Heart failure (HF) is associated with increased risk of dementia and dementia is an independent predictor of mortality and hospitalization in HF patients. Angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may lower the risk of dementia by regulating the renin angiotensin system in the brain. Given the significant clinical impact of dementia associated with HF and the current urgency for effective treatments to reduce the incidence of dementia, the present study examines the effectiveness of ACEIs/ARBs that are widely prescribed for the treatment of HF

**Methods:** This retrospective, longitudinal study used a cohort of patients with HF identified from a local Medicare advantage prescription drug plan to examine incidence of dementia with up to 3 years of follow up period. Multivariable time dependent Cox model and inverse-probability-of-treatment weighting (IPTW) of marginal structural model were used to estimate the risk of developing dementia controlling for sociodemographic factors, comorbidities, comedications, appropriate laboratory measures, and potential time-varying confounding affected by previous treatment (hospitalization). Adjusted dementia rate ratios were estimated among current and former ACEI/ARB users, as compared with nonusers.

**Results:** The study included a total of 8062 HF patients (mean age 74.47 ±9.21 years) of which 1135 (14.08 %) patients were diagnosed with dementia during the median follow up of 22 months. Using the time dependent Cox model, the adjusted dementia rate ratios (95% confidence interval) among current and former users were 0.90 (0.70 to 1.16) and 0.89 (0.71 to 1.10). Use of IPTW resulted in similar effect estimates (95% conservative confidence interval) of

0.99 (0.74 to 1.32) among current users and 0.80 (0.59 to 1.08) for former users as compared with the nonusers.

**Conclusion:** This study found no difference in risk of dementia among the current and former users of ACEI/ARB as compared with the nonusers in an already at-risk HF population.

## Introduction

Heart failure and Dementia are common medical conditions in older adults.[1] More than 5.5 million adults have heart failure (HF) in the United States (US) and the incidence approaches 10 per 1000 population after 65 years of age.[2] Despite a decline in cardiovascular mortality in developed countries over the last three decades, the burden of heart failure (HF) has risen.[3, 4] Dementia is an independent predictor of increased mortality in HF patients.[5-8] One in six individuals older than 70 have dementia with prevalence increasing exponentially with advanced age. It is estimated that the number of dementia cases in 2050 will increase threefold compared with the year 2000.[9] Alzheimer's Disease (AD) is the most common followed by vascular dementia (VaD) and other forms of dementia. There is considerable overlap emerging in the risk factors and pathogenesis of vascular dementia and Alzheimer's disease.[10]

HF is associated with more than an 80% increase in the risk of dementia and AD.[1, 11, 12] The probable biological pathways linking HF to dementia, and AD in particular, include considerably impaired cerebral circulation from HF, clinical and silent brain infarcts, leukoaraiosis, and cerebral thrombosis for which HF is a risk factor. A number of vascular comorbidities such as atrial fibrillation, hypertension, dyslipidemia and diabetes mellitus common in HF are linked to dementia.[13-17]. Another potential pathway is through the impaired cerebrovascular reactivity due to HF that could further aggravate hypoperfusion-related cerebral ischemia and neurodegeneration.[1, 16] It is important to note that "vascular risk factors" appear to increase the risk of AD through non-vascular mechanisms. So, while all of the vascular mediated mechanisms listed are plausible and possible, it is thought that other non-vascular mechanisms are probably the link between these risk factors and AD.

Numerous studies have found that hypertension is a risk factor for dementia.[18-20] Therefore, its control in HF patients should be beneficial in reducing the incidence of dementia.[21] Our previous work showed that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) were better than other anti-hypertensive agents in reducing the risk of dementia in elderly diabetic patients. There are plausible biological rationales to support the protective effects of ACEIs/ARBs in dementia. Recent findings support that the brain has its own renin–angiotensin system, and ACEI/ARB may regulate it to show neuroprotection. ACEIs/ARBs have been shown to restore normal cerebral autoregulation, reverse inflammatory reactions, decrease neuronal cell death, and have antiplatelet aggregating and atrial antifibrillatory effects. [22-24] However, there are studies that found no association with use of ACEIs/ARBs and risk of dementia.[25, 26] To our knowledge there is no study in HF patients that assessed the effect of ACEIs/ARBs on time to dementia diagnosis. Moreover, literature showed that ACEIs/ARBs have different effect on cognitive impairment in patients with and without HF[27] and dementia significantly increased the risk of hospitalization and mortality in HF patients.[5, 7, 8] Given the significant clinical impact of dementia associated with HF and the current urgency for effective treatments to reduce the incidence of dementia, the present study examines the effectiveness of ACEI/ARB that are widely prescribed for the treatment of HF.

The key challenge in comparison of true treatment (causal) effects in an observational study is the presence of confounding, especially confounding by indication for treatment. Furthermore, in longitudinal studies involving chronic illnesses such as HF, some confounders change with time during the follow-up. A model that allows incorporation of time-varying confounders is the extended Cox model. However, it has been argued that this model is not sufficient to give causal effect estimates in presence of time-dependent confounders that are affected by previous treatment.[72, 87] To estimate the causal effect of treatment on outcome in the

presence of such confounding, marginal structural models (MSM) have been proposed. [88] In the present study, we have considered occurrence of hospitalization to be a time-dependent confounder affected by previous treatment. Physicians may adjust ACEI/ARB therapy after occurrence of a hospitalization that may be indicative of decompensation in overall health that could herald increased risk of dementia. However, (prior) ACEI/ARB therapy should benefit patients and reduce their risk of hospitalization. Therefore, hospitalization may be time dependent confounder in this study, because it is predictor of subsequent treatment, predicted by previous treatment, and may be associated with risk of dementia. This relationship is illustrated in the figure 1.

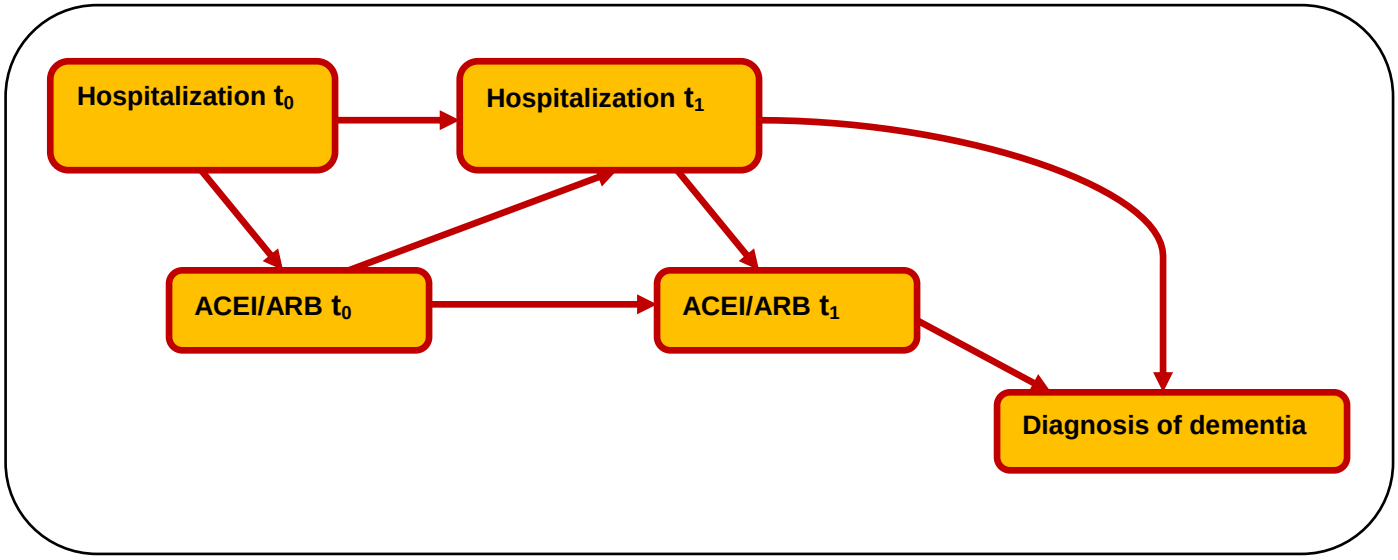



**Figure 1.** Illustration of time-dependent confounding of ACEI/ARB use and risk of dementia by hospitalization

The goal of this study is to test the causal effect of ACEIs/ARBs on reducing dementia in patients with heart failure using extended Cox model and Marginal structural model to account for time-dependent confounding by hospitalization.

## Methods

*Data source*

The study design was a retrospective longitudinal cohort of all HF patients in a Medicare advantage prescription drug (MAPD) plan in Texas from January 1, 2008, to December 31, 2011. Several computerized data files including membership file, member summary file, institutional claims file, professional claims file, quest lab, CCMS and pharmacy file were used. Membership and member summary files include demographic, severity scores and cost data for beneficiaries for each year. Institutional claims include information on all inpatient claims. The files contain diagnostic information in the form of International Classification of Diseases, Ninth Revision (ICD-9) codes, and procedure information in form of Current Procedural Terminology (CPT) codes. Professional claims contain information on all outpatient encounters. The files contain diagnostic information in the form of ICD-9-CM codes and procedure information in form of CPT codes. Quest lab files contain 153 applicable lab tests that include low-density lipoprotein (LDL-C), hemoglobin A1c (HbA1c) and creatinine. CCMS file include the hospitalization records, date of admission, date of discharge and length of stay. Pharmacy files contain Part D pharmacy data provided by pharmacy benefits manager. The pharmacy records include patient and drug identifying information, fill dates, days of supply, quantity dispensed and dosing information for each prescription filled.

*Selection of patients*

Patients were included in the study sample if they had at least one claim after the index date and diagnosed with HF (ICD-9-CM 402.01, 402.11, 402.91, 415.0X, 416.9X, 425.4X-425.9X, 428.XX, 429.4X, 785.51) between January 1, 2008, and December 31, 2011. Patients were excluded if they were diagnosed with dementia or died before the index date. Index date was defined as January 1, 2009 for patients that had HF diagnosis on or before January 1, 2009 and

their coverage prior to January 1, 2008; date of HF diagnosis for patients that had 1 or more years of records prior to HF diagnosis or date at which the HF patients had at least 1 year prior records. Finally, records with missing values except for the laboratory measures were deleted from the final sample, as suggested by Little and Rubin (1989).[79]

Outcome measure

Time to dementia diagnosis. Dementia was defined based on the occurrence of any relevant ICD-9-CM codes in the inpatient or outpatient records from the index date. The diagnosis of dementia was examined through December 31, 2011. ICD-9 codes to identify dementia diagnosis are given in Appendix A.[18, 19]

Exposure

A patient's exposure to ACEI/ARB was assessed for the study period (01/01/2009 -12/31/2011). Exposure was classified on a monthly basis by assessment of the days' supply of the filled prescription until the termination of days' supply and the fill date of the next filled prescription occurs. Every person-month during study follow-up was classified according to use of ACEIs/ARBs. Current use was defined as use during the month when the prescription for ACEIs/ARBs covered 15 or more days. Former use was defined as use during the months after the current use or when prescription for ACEIs/ARBs covered less than 15 days. Non use was defined as no prescribed use of ACEIs/ARBs or prescription covered less than 15 days in the month being classified or any preceding months. Former users and nonusers could become current users of ACEIs/ARBs during follow-up. Exposure to ACEI/ARBs was therefore time-varying or time-dependent, and could change over the course of follow-up.

Average daily dose (ADD) and achievement of targeted dose. ADD was calculated at the baseline as the total quantity of ACE/ARB divided by the available days of ACEI/ARB therapy

during the 6-month pre-index period. Dose was standardized to 20 mg of enalapril equivalent. After calculating ADD for each patient, a categorical variable for attainment of targeted dose was created as below targeted dose and at or above targeted dose. [89]

Covariates

The variation in survival rates may be associated with the time independent socio-demographic factors, treatment factors and clinical factors, therefore the study included 43 such covariates. Socio-demographic factors included age and gender. Treatment factors included various co-medications taken 1 year prior to the index date. We included diuretics (thiazide diuretics, potassium sparing diuretics and loop diuretics), digitalis glycosides, statins, calcium channel blockers (CCBs), beta blockers (BBs), vasodilators, anti-arrythmics, alpha blockers, insulin, oral hypoglycemics and non statin lipotropics. Clinical factors included 22 co-morbid conditions[70, 80, 81] and appropriate laboratory measures like serum creatinine, low-density lipoprotein (LDL-C), hemoglobin A1c (HbA1c). Severity of illness could not be assessed by ejection fraction (EF) or New York Heart Association (NYHA) HF classification due to lack of information in the database. Instead we used number of years in the cohort and prior hospitalization as a substitute for HF severity[70, 71]. We also included number of all drugs taken, number of co-morbid conditions and Centers for Medicare and Medicaid Services (CMS) risk score to account for medication burden and disease severity. The CMS risk score is calculated based on data taken from a large pool of beneficiaries to estimate the average predicted costs for each of the component factors (e.g., age-sex, low income status, individual disease groups). It consists of 189 disease classifications for use in risk adjusting of clinical outcomes in Medicare populations.[19]

In addition to the time independent covariates, the time dependent covariates considered for the study were concurrent hospitalization, cumulative duration of ACEI/ARB use and adherence defined on a monthly basis. A patient was considered hospitalized in a particular month if she was admitted to the hospital in that month. If the length of stay in hospital was more than 30 days, then the patient was considered hospitalized for two consecutive months and so on. Duration of use was calculated as cumulative duration of use by summing the duration of all prescriptions and updated monthly. Adherence-as medication possession ratio (MPR) was calculated as follows:

MPR= (Total months supply) / time available)*100.

A dichotomous variable was created as less than 80% MPR and greater than or equal to 80%MPR( [81] on monthly basis.

*Statistical analysis*

Analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC). Bivariate associations between the predictor variables and outcomes were tested using the chi-square test for categorical variables and the *t test* for continuous variables. Two different approaches were used to test the effect of ACEI/ARB use on the risk of the dementia diagnosis. First a time-dependent Cox model was developed and second a marginal structural Cox model using inverse probability weights was constructed.

Time-dependent Cox model

Crude dementia rates for baseline ACEIs/ARBs use versus nonuse were compared. Kaplan–Meier method was used to estimate unadjusted dementia diagnosis by baseline use of ACEIs/ARBs, and the log-rank test was used to compare the groups. Next a multivariable time-dependent Cox model of time to dementia diagnosis was constructed. The independent

variables used in the Cox regression were 43 time-independent factors like socio-demographic factors, treatment factors and clinical factors. And time dependent factors updated monthly like exposure groups, duration of use, medication possession ratio and hospitalization. Patients were censored if they did not reach the outcome till December 31, 2011 (end of the study) or if the patient died before dementia diagnosis. Hazards ratios (HR)/rate ratios were obtained from the model after adjusting for the covariates mentioned above. Hospitalization may be a time dependent confounder in the present study. It is an intermediate variable affected by previous treatment and predicting future treatment and also an independent risk factor for dementia. Thus, simply adding this variable in the time dependent Cox model may introduce bias and cannot provide causal effect of ACEI/ARB on dementia [72, 87]

Marginal structural Cox model

Marginal structural Cox model using inverse-probability-treatment-weights (IPTW) were used to estimate the causal effect of ACEI/ARB use (current use and former use) versus nonuse on dementia diagnosis. In IPTW a pseudopopulation is created that consists of “copies” of original subjects who account not only for themselves but for subjects with similar characteristics who received the other exposure.[90] In time independent exposure IPTW creates a pseudopopulation in which all subjects are considered conditionally exchangeable by achieving a balance between the treated and non-treated groups on the baseline covariables at the start of the study.[70, 71] Whereas in longitudinal studies with time varying exposure , the marginal structural models (MSMs) use the IPTW that is updated at various time points to achieve the balance between the groups not only at baseline but also at different time points. Therefore MSM allows controlling for effects of time-dependent confounders that predict the subsequent treatment and that are predicted by previous treatment.[91]

The MSM using IPTW is related to propensity scoring, where the probability that the subject received his own observed treatment, given covariables.[73, 92, 93] The IPTW is the inverse of the propensity scores that are calculated using multinomial logistic regression in case of multiple treatment settings (treatments A, B and control). [70, 71] If the propensity score distribution has large variability (possibly because some covariates are highly correlated with treatment) then the treatment patterns will have extremely large weights [91] Robins *et al.*[88] and Hernán *et al.*[94] recommend replacing the IPTW with stabilized weights to reduce this variability and ensure the estimated treatment effect remains unbiased.[91] These stabilized weights were calculated using two components, the treatment history weights and the censoring history weights.[94, 95]

Thus, in MSM, using stabilized weights, the first step was to create the treatment history weights at various time intervals. Treatment history weights for each month were calculated as conditional probability of receiving the observed treatment based on the treatment history (treatment in prior month, duration of use and adherence) and the baseline covariates divided by conditional probability of receiving the observed treatment based on the treatment history and the baseline covariates and also the time dependent covariates (hospitalization, prior month hospitalization).[72, 94] The second step was to calculate the censoring history weight to adjust for censoring by mortality or end of the study. The censoring history weights were calculated by similar procedure as treatment history weights. Next the above two calculated weights were multiplied to create stabilized weights for each subject in each time period.[95] For the final step to estimate the probability of having observed outcome, dementia diagnosis, among those with observed treatment histories, a weighted pooled logistic regression model was estimated, treating each person-month as an observation. The model was also controlled for all baseline covariates. Under the assumptions of positivity, consistency, no model misspecification, and no

unmeasured confounding, the treatment effects in this model can be interpreted as causal effects.[72] To correct the correlation between subjects arising due to repeated measures taken on the same individual, we used generalizing estimating equations with robust standard errors from an independent working correlation matrix to fit the weighted pooled logistic regression model.[87]

The estimates obtained from MSM were compared with the hazards ratios obtained from time-dependent Cox model to determine the bias due to presence of time-varying confounding factors (hospitalization).

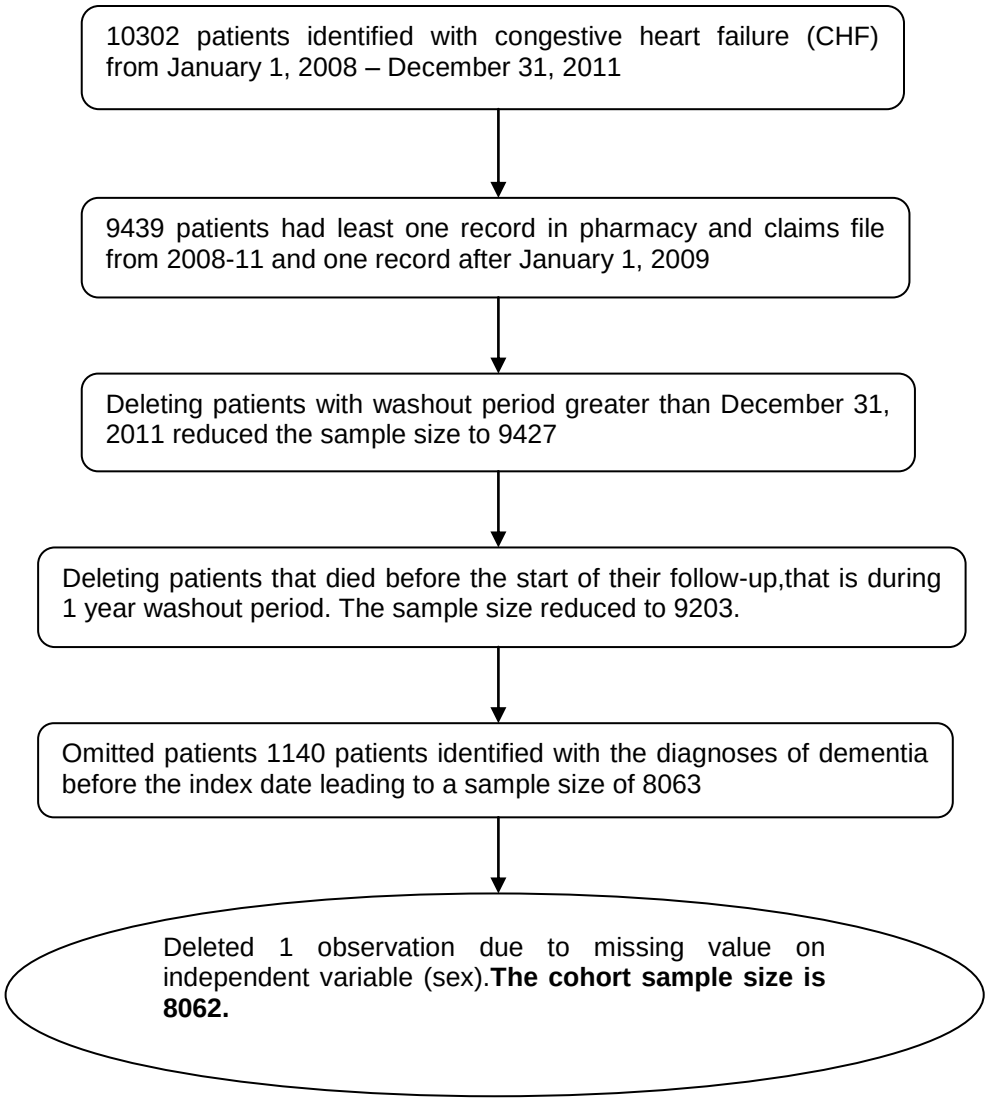
Sub-group analysis

Two separate subgroup analysis were carried out that restricted the age group to >= 65-years and that used a new user design for drug exposure.[96] The study was approved by the Institutional Review Board of University of Houston.

## Results

The process of selection of patients for the analysis is outlined in the Fig. 2. A total of 8063 patients with HF were identified that met inclusion and exclusion criteria. There was one record with missing data on gender and was excluded from analysis. Thus, the study sample comprised 8062 HF patients of which 1135 (14.08 %) patients were diagnosed with dementia over a follow up to 36 months period between January 01, 2009 and December 31, 2011. The median length of follow-up for the cohort was 22 months for a total follow-up of 180 381 patient months.

**Figure 2** Derivation of the study sample.

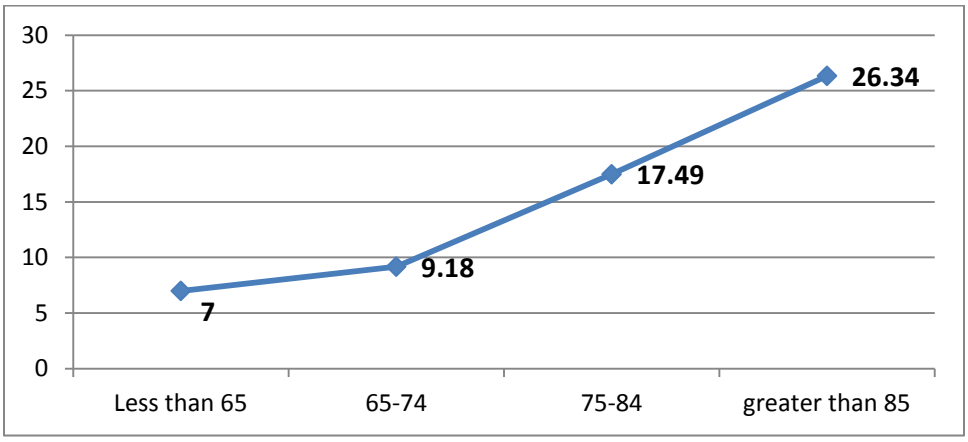



Patient characteristics

Table 1 compares the baseline characteristics of patients with and without dementia. The mean age (± standard deviation) of the HF cohort was 74.47 (±9.21) years. Patients with dementia

were older (78.23 ± 8.53 years) than those without dementia (73.85 ± 9.17 years, *P* < .0001). The incidence of dementia increased with age from 7.00% in the < 65 -year age group to 9.18% in the 65-74, to 17.49% in the 75-84 and to 26.34% in the >85-year age groups (Figure 3). Sex was not associated with a diagnosis of dementia. (*P* =0.199).

**Figure 3.** Incidence of dementia among different age-groups




About 39% patients had more than 5 co-morbid conditions. Of the 22 co-morbid conditions, top five co-morbid conditions were hypertension (87.14%), hyperlipidemia (60.33%), ischemic heart disease (46.81%), diabetes (45.19%) and chronic lung disease (37.35%). Hypertension (87.31% vs 87.11%, *P*= 0.849), diabetes (47.31% vs 44.48%, *P*= 0.121) and chronic lung disease (37.53% vs 37.32%, *P*=0.890) had similar percent of patients with and without dementia, but the two groups differed significantly on hyperlipidemia (52.16% vs 61.67%, *P* <.0001*)* and Ischemic heart disease (49.96% vs 46.30%, *P*= 0.022*)*. Approximately 42% of the patients had prior hospitalization, which was significantly associated with dementia (*P*<.0001). Increasing years with HF and higher comorbid conditions were each associated with a higher incidence of dementia (*P*< .0001), however no statistical significance was noted with CMS risk score in regards to diagnosis of dementia (*P*= 0.236).

In unadjusted analysis, patients taking statins (*P*= 0.012) had a lower incidence of dementia, whereas those taking CCBs (*P*=0.0001), digoxin (*P*=0.007*)* and alpha-blockers (*P*= 0.006) had a higher incidence of dementia. The ADD for baseline use of ACEI/ARB (enalapril equivalent) was 21.44 (±12.6) mg and 64.97% (n=2978) patients received the target dose among the baseline users of ACEI/ARB (n=4584).

**Table 1.** CHF Patient Characteristics -8062 patients

| | Total N(%) | Dementia N(%) | No Dementia N (%) | *p-value* |
|---|---|---|---|---|
| **Patient count** | 8062(100) | 1135(14.08) | 6927(85.92) | |
| **Age in years** mean (SD) | 74.47(9.21) | 78.23(8.53) | 73.85(9.17) | <.0001* |
| **Age groups** | | | | |
| < 65 | 929 (11.52) | 65(5.73) | 864(12.47) | <.0001* |
| 65-74 | 3128(38.80) | 287(25.29) | 2841(41.01) | |
| 75-84 | 3071(38.09) | 537(47.31) | 2534(36.58) | |
| >=85 | 934(11.59) | 246(21.67) | 688(9.93) | |
| **Gender** | | | | |
| Males | 3786(46.96) | 513(45.20) | 3273(47.25) | 0.199 |
| Females | 4276(53.04) | 622(54.80) | 3654(52.75) | |
| **CMS Risk Scores** mean (SD) | 1.60(1.12) | 1.58(1.08) | 1.62(1.20) | 0.236 |
| **Co-morbidities** | | | | |
| Hypertension | 7025(87.14) | 991(87.31) | 6034(87.11) | 0.8488 |
| Ischemic Heart Disease | 3774(46.81) | 567(49.96) | 3207(46.30) | 0.022* |
| Conduction Disorders | 1334(16.55) | 196(17.27) | 1138(16.43) | 0.480 |
| Cardiac Arrhythmias | 1960(24.31) | 304(26.78) | 1656(23.91) | 0.036* |
| Valvular Heart Disease | 1776(22.03) | 271(23.88) | 1505(21.73) | 0.105 |
| Cerebrovascular Disease | 1286(15.95) | 254(22.38) | 1032(14.90) | <0.0001* |
| Chronic lung disease | 3011(37.35) | 426(37.53) | 2585(37.32) | 0.890 |
| Diabetes | 3643(45.19) | 537(47.31) | 3106(44.84) | 0.1206 |
| Renal disease/Renal Failure | 2234(27.71) | 359(31.63) | 1875(27.07) | 0.001* |
| Disorders of upper GI and Liver | 689(8.55) | 106(9.34) | 583(8.42) | 0.303 |
| Non-Skin Malignancies | 822(10.20) | 124(10.93) | 698(10.08) | 0.381 |
| Anemia & Coagulation Disorders | 1804(22.38) | 290(25.55) | 1514(21.86) | 0.006* |
| Decubitus and LE ulcers | 428(5.31) | 86(7.58) | 342(4.94) | 0.0002* |
| Thyroid Disorders | 1395(17.30) | 217(19.12) | 1178(17.01) | 0.081* |
| Sleep Apnea | 362(4.49) | 42(3.70) | 320(4.62) | 0.166 |
| Alcohol Related Disease | 82(1.02) | 6(0.53) | 76(1.10) | 0.077* |
| Other Psychiatric Disorders | 1300(16.13) | 242(21.32) | 1058(15.27) | <0.0001* |
| Pulmonary Heart Disease | 431(5.35) | 64(5.64) | 367(5.30) | 0.636 |
| Thromboembolism | 448(5.56) | 70(6.17) | 378(5.46) | 0.333 |
| Hyperlipidemia | 4864(60.33) | 592(52.16) | 4272(61.67) | <.0001* |
| Peripheral arterial disease | 1730(21.46) | 296(26.08) | 1434(20.70) | <0.0001* |
| **Prior hospitalization** | 3379(41.91) | 572(50.40) | 2807(40.52) | <.0001* |
| **Number of co-morbid conditions** | | | | |
| Less than or equal to 5 | 4935(61.21) | 635(55.95) | 4300(62.08) | <.0001* |

| | Total N(%) | Dementia N(%) | No Dementia N (%) | *p-value* |
|---|---|---|---|---|
| More than 5 | 3127(38.79) | 500(44.05) | 2627(37.92) | |
| **Years with HF** | | | | |
| 0 | 3923(48.66) | 420(37.00) | 3503(50.57) | <.0001* |
| 1 | 1677(20.80) | 233(20.53) | 1444(20.85) | |
| 2 | 1164(14.44) | 210(18.50) | 954(13.77) | |
| =>3 | 1298(16.10) | 272(23.96) | 1026(14.81) | |
| **Co-medications** | | | | |
| Beta Blocker Use | 4478(55.54) | 633(55.77) | 3845(55.51) | 0.869 |
| CCB Use | 2708(33.59) | 438(38.59) | 2270(32.77) | 0.0001* |
| Digoxin Use | 813(10.08) | 140(12.33) | 673(9.72) | 0.007* |
| Vasodilators Use | 1526(18.93) | 233(20.53) | 1293(18.67) | 0.138 |
| Diuretics Use | 5044(62.57) | 713(2.82) | 4331(62.52) | 0.849 |
| Alpha blockers use | 388(4.81) | 73(6.43) | 315(4.55) | 0.006* |
| Anti Arrythmic use | 422(5.23) | 67(5.90) | 355(5.12) | 0.275 |
| Insulin use | 1137(14.10) | 179(15.77) | 958(13.83) | 0.0816 |
| Hypoglycemic use | 2475(30.70) | 358(31.54) | 2117(0.56) | 0.5069 |
| Non- statin lipotropic use | 1242(15.41) | 154(13.57) | 1088(15.71) | 0.064 |
| ACEIs/ARBs at baseline | 4584(56.86) | 623(54.89) | 3961 (57.18) | 0.148 |
| Statins | 4249(52.70) | 559(49.25) | 3690(53.27) | 0.012* |
| **Number of drugs** | | | | |
| Less than or equal to 3 | 3737(46.35) | 529(46.61) | 3208(46.31) | 0.853 |
| More than 3 | 4325(53.65) | 606(53.39) | 3719(53.69) | |
| **Serum creatinine level** | | | | |
| <1.5 | 4484(55.62) | 628(55.33) | 3856(55.67) | <.0001* |
| 1.5-2.5 | 723(8.97) | 137(12.07) | 586(8.46) | |
| >2.5 | 179(2.22) | 33(2.91) | 146(2.11) | |
| Unknown | 2676(33.19) | 337(29.69) | 2339(33.77) | |
| **Hemoglobin A1-c** | | | | |
| <=7 | 1859(23.06) | 282(24.85) | 1577(22.77) | 0.003* |
| >7 | 849(10.53) | 145(12.78) | 704(10.16) | |
| Unknown | 5354(66.41) | 708(62.38) | 4646(67.07) | |
| **Low-density lipoprotein** | | | | |
| <100 | 2692(33.39) | 428(37.71) | 2264(32.68) | 0.001* |
| 100-129 | 1073(13.31) | 144(12.69) | 929(13.41) | |
| >129 | 650(8.06) | 81(7.14) | 569(8.21) | |
| Unknown | 3647(45.24) | 482(42.47) | 3156(45.69) | |

* indicates statistically significant difference

LE, lupus erythematosus; HF, heart failure; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitors;ARB, angiotensin receptor blockers

Time-dependent Cox model

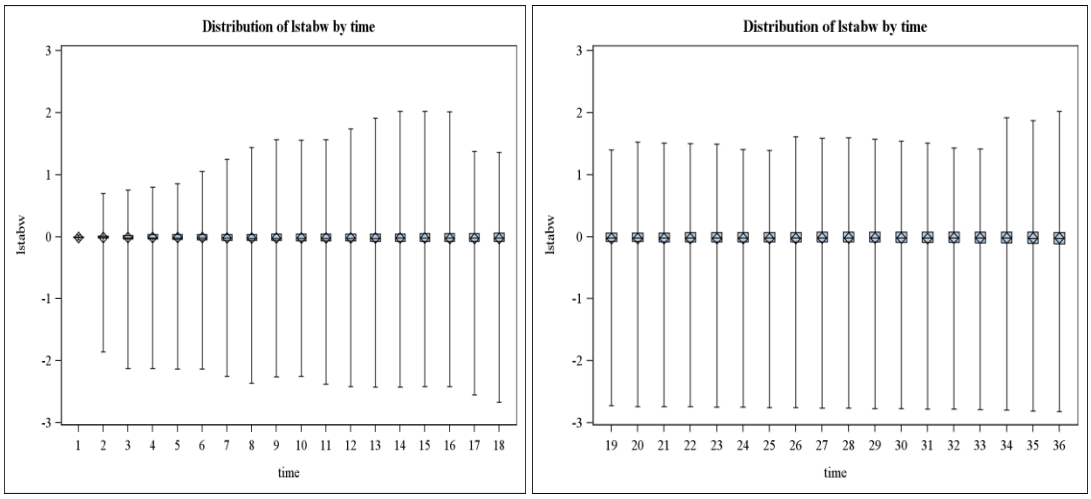
There were no significant differences in the crude dementia rates for baseline users of ACEI/ARB (13.59%) vs nonusers (14.72%) (*P*= 0.148). However, the Kaplan Meier curve showed that unadjusted survival was significantly different across baseline ACEI/ARB users vs

nonusers (*P*=0.028 for log rank test). Multivariable time-dependent Cox model found that as compared with the nonusers, the adjusted hazards ratio did not differ significantly among the current users of ACEIs/ARBs (HR, 0.90; 95% confidence interval [CI], 0.70 to 1.16) or among former users (HR, 0.89; 95% CI, 0.71 to 1.10) (Table 2).

Marginal structural Cox model

Figure 3 presents the distribution of the final weights, which combine information on ACEI/ARB and censoring history, for the follow-up times (a logarithmic transformation was applied for display purposes only). The distribution of stabilized weights was symmetric and centered around 1 at all times (mean = 1.007, SD = 0.228).

**Figure 3.** Distribution of stabilized weights




After adjusting for the time-dependent confounder (hospitalization) in addition to the other confounders (listed in table 1) and applying stabilized weights to a pooled logistic regression, the estimated causal dementia rate ratio was 0.99 (95% conservative confidence interval-0.74 to 1.32) for current users and 0.80 (95% conservative confidence interval-0.59 to 1.08) for former users. Thus under our assumptions of positivity, consistency, no model misspecification, and no unmeasured confounding, ACEI/ARB current use or former use does not appear to

decrease the risk of dementia.(Table 2) These estimates were similar to the hazards ratio obtained from the standard time-dependent Cox model.

Sub-group analysis

We performed two sub-group analyses to test the robustness of study findings (Table 2). To assess for the possible bias from inclusion of subjects <65-years of age ( patients with end stage renal disease,ESRD or disability), we restricted our analysis to all persons 65 years of age or older. Findings were essentially identical to those of the primary analysis for both time dependent Cox model (Current users, HR, 0.89; 95% CI, 0.68 to 1.15; former users, HR, 0.89; 95% CI, 0.71 to 1.12) and marginal structural Cox model (Current users, rate ratio, 0.95; 95% CI, 0.70 to 1.28; former users, rate ratio, 0.76; 95% CI, 0.55 to 1.06). In the analyses that included only the new users (defined as no use of ACEI/ARB during the 6 months prior to the index date), we found no association between ACEI/ARB use (current and former) and risk of dementia.

**Table 2.** Adjusted rate ratio, 95% Confidence interval and p-value for time-dependent Cox model and IPTW estimation of marginal structural Cox model

| Effect | Rate Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| **Primary Analysis for all subjects in HF cohort** | | | |
| Time-dependent Cox model | | | |
| Current users vs nonusers | 0.90 | 0.70 - 1.16 | 0.419 |
| Former users vs nonusers | 0.89 | 0.71- 1.10 | 0.275 |
| IPTW estimation of marginal structural Cox model | | | |
| Current users vs nonusers | 0.99 | 0.74- 1.32 | 0.954 |
| Former users vs nonusers | 0.80 | 0.59- 1.08 | 0.145 |
| **Analysis restricted to subjects 65 years of age or older** | | | |
| Time-dependent Cox model | | | |
| Current users vs nonusers | 0.89 | 0.68 - 1.15 | 0.357 |
| Former users vs nonusers | 0.89 | 0.71- 1.12 | 0.321 |
| IPTW estimation of marginal structural Cox model | | | |
| Current users vs nonusers | 0.95 | 0.70- 1.28 | 0.720 |
| Former users vs nonusers | 0.76 | 0.55- 1.06 | 0.102 |
| **Analysis restricted to new users of ACEI/ARB** | | | |
| Time-dependent Cox model | | | |
| Current users vs nonusers | 1.18 | 0.81 - 1.74 | 0.378 |

| Effect | Rate Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| Former users vs nonusers | 0.89 | 0.64- 1.22 | 0.464 |
| IPTW estimation of marginal structural Cox model | | | |
| Current users vs nonusers | 0.96 | 0.70- 1.30 | 0.774 |
| Former users vs nonusers | 0.88 | 0.60- 1.28 | 0.504 |

## Discussion

This study tested the hypothesis that ACEI/ARB would reduce the risk of dementia in patients with HF. These results demonstrate that with the current or former use of ACEI/ARB there was no significant difference in the risk of dementia as compared with the nonuse. Unbiased estimation of the effect of treatment in an observational study requires adjustment for time-dependent confounding.[97] Standard time dependent Cox model that incorporate time varying variables give biased estimates of the true effect of treatment in presence of these time varying confounders. Therefore, to estimate the causal effect of ACEI/ARB on risk of dementia we used both a time dependent Cox model and IPTW estimation of a marginal structural Cox model. The rate ratios obtained from the standard Cox model were similar to that of the MSM, indicating that the mediation by the time varying confounder (hospitalization) considered in the study was minimal.

We performed sub group analyses to test the robustness of our findings. We restricted our analysis to all persons 65 years of age or older to assess for the possible bias from inclusion of subjects <65-years of age, with ESRD or disability. We also performed an analysis restricted to new users to address bias that would be introduced from the inclusion of prevalent users in the cohort.[96] The findings from the sub group analyses were essentially identical to those of the primary analysis.

To the best of our knowledge, this is the first study to examine the effect of ACEI/ARB use on risk of dementia in HF patients. One observational study by Zuccala et al.[27] assessed the

effect of treatment with ACEI on cognitive improvement in HF patients. The study found that starting the treatment with ACEIs was significantly associated with improvement in cognitive performance (odds ratio, 1.57; 95% CI 1.18–2.08) among patients with HF. Our conclusion differs from theirs in reporting no difference in effectiveness of ACEIs/ARBs use versus nonuse. One reason for this could be the outcome considered, Zuccala et al. examined cognitive performance whereas our study assessed the risk of dementia. However, studies have shown that mild cognitive impairment is a strong predictor of dementia and AD.[98] Another reason could be the median follow up time, Zuccala et al had a very short median follow up time of 13 days whereas our study had a considerably longer median follow up time of 22 months. Third reason could be the study population and the exposure group considered, Zuccala et al failed to mention whether the patients included were incident or prevalent HF cases and considered the effect of ACEI therapy only whereas our study represented real world practice settings that included a mixture of incident and prevalent CHF cases. Also the exposure group considered was use of either ACEI or ARB.

There are several theoretical reasons through which ACEI/ARB could offer neuroprotection. ACEI/ARBs in addition to controlling co-morbid hypertension can increase the impaired cerebral blood flow that is common in AD. This effect can be attributed to the improvement in left ventricular systolic function with use of these drugs.[27, 99-101] HF is associated with increased angiotensin II activity in the brain and angiotensin II mediates inhibition of acetylcholine release and produces endothelial dysfunction in the cerebral circulation.[27, 102] Thus inhibition of the signaling by angiotensin II might provide beneficial effects in AD. ACEI/ARB may inhibit or block the angiotensin II mediated activities as well as interrupt the upregulation of inflammatory nitric oxide synthase isoenzymes that are associated with AD and dementia.[22, 99] Despite these probable pharmacological mechanisms, our results suggest no statistical difference in the

effectiveness among current and former users as compared with nonusers in reducing dementia in HF.

The literature on effect of ACEI/ARB use on risk of dementia in population without HF is mixed. Some prior studies have shown a statistically significant decrease in risk of AD and other dementia among persons receiving ACEI/ARB therapy. In a 1-year, prospective, randomized, parallel-group cohort trial, Ohrui et al[103] found that brain penetrating ACEI decreased the progression of AD significantly as compared with a non penetrating ACEI or CCB. The Heart Outcomes Prevention Evaluation (HOPE)[104] Study and the Perindopril Protection Against Recurrent Stroke Study (PROGRESS)[105] demonstrated a 41% reduction in cognitive decline associated with stroke and a 34% reduction in dementia among patients with recurrent stroke with the use of an ACEI. The post-hoc analysis of Study on Cognition and Prognosis in the Elderly (SCOPE) found that the cognitive decline in the ARB group (candesartan) was significantly lower (RR, 0.49), suggesting that candesartan is neuroprotective.[106] Our prior work did find a significant association between ACEIs, ARBs and risk of dementia in patients with diabetes. As compared to the non users, there was 24% and 18%, decrease in the risk of dementia in subjects on ARB and ACEI respectively.[18]

In contrast other studies have failed to show a lower risk of AD and dementia with ACEI/ARB use. A study by Khachaturian et al[25] examined the relationship of antihypertensive drugs use and the incidence of AD in an elderly population (age≥ 65 years) of Cache County, Utah. This observational study involved more than 3000 participants and revealed increased protection from Alzheimer's disease with the use of antihypertensive medication as a whole. However; the study failed to show any association with the use of ACEIs and risk of dementia. Hanon et al[107] conducted a cross-sectional study of 1241 hypertensive patients from a cohort of elderly

patients who reported memory loss and were attending a geriatric memory clinic.[20] No significant associations were found with the use of ACEI or ARBs and incidence of AD. None of the aforementioned studies was done to assess the effects of ACEI/ARB use on an already-at-risk HF population.

A possible explanation for our findings is that follow-up period was relatively short with median length of follow-up of 22 months to observe incident dementia. However this study found significant increases in dementia rates as age increased, thus giving face validity to the study results (Figure 3).[18] Another reason could be confounding by severity of illness, as we could not account for information on ejection fraction and NYHA HF classification. However, we attempted to control for this by adjusting for the number *of* years with HF, number of all medicine, and prior hospitalization of the patients, as in other large studies of HF patients.[70, 71, 80] We also adjusted for 21 co-morbidities, CMS risk scores and accounted for time‐dependent confounding by indication by adding monthly hospitalization records as a severity of illness factor in MSM. Finally, our findings are a cross-sectional view of real clinical practice in a cohort of HF patients with a follow up to 3 years for a long term condition. These results may not be generalizable to patients without HF as previous literature shows an interactive effect between use of ACEI and HF on cognitive impairment.[27]

Our study possesses several unique strengths. Our cohort, with a high prevalence of comorbidities and abundantly prescribed comedications, adequately represents the patient population in real‐world practice settings. Our study uses some important clinical factors like the serum creatinine, HbA1c and LDL-C values that are not usually recorded in retrospective databases. Use of dose information of the ACEIs/ARBs strengthens the results as it plays an important role in predicting the clinical outcomes in HF patients.[108] We addressed the issue of

non‐randomized treatment allocation in an observational study by creating a pseudo‐randomized sample by applying inverse-probability-treatment-weights to the sample.[72] As time-dependent Cox model cannot address the issue of time dependent confounding by indication we also carried out the analysis using MSM. Our results were robust independently of the analytical strategy and the sub group analyses performed.

The interpretation of results of this study should be made in light of several limitations. First, for MSM to have valid estimates we make an assumption of no unmeasured confounding, which remains untestable. However, it is likely that any potential unmeasured confounders would be somewhat correlated with the numerous sociodemographic, clinical and severity of illness measures that were measured, thus reducing residual confounding. In addition to lacking information on disease severity (ejection fraction and NYHA HF classification), the ICD-9-CM codes used to identify HF cannot differentiate between systolic and diastolic left ventricular dysfunction. Hogg et al.[109] estimated patients with HF to be equally distributed between systolic and diastolic dysfunction, suggesting it is reasonable to consider them same and thus studying effects of treatment on all HF patients.[89] Distinguishing vascular from Alzheimer-type dementia is probably not reliable in our data. Also, we could not control for potential risk factors for dementia, such as race, education, diet, smoking, and alcohol use. Finally, dispensed prescriptions were considered as actually consumed. However, in general, pharmacy claims are demonstrated to be an accurate measure of prescription drug consumption.[110] To the extent possible, measures of adherence or persistence of use were created in a cumulative and time-varying manner during follow-up to strengthen analyses.

In conclusion, in absence of randomized clinical trials, appropriate adjustment for time-varying confounding by indication may provide the best evidence to estimate the treatment effect in

observational studies. This exploratory study using time-dependent Cox model and MSM found no association between the current and former use of ACEI/ARB as compared with the nonuse in a HF cohort. However, we note that MSM provided similar effect estimates to the time dependent Cox model indicating that the mediation by time-dependent confounder considered in the study was minimal. Further research needs to be done in HF population in which other measures like changing blood pressure or ejection fractions could be handled as time varying confounders. Also, it would be interesting to compare the effects of these drugs in patients with and without HF.

***Appendix A***

| Dementia Diagnostic Codes | |
|---|---|
| ICD-9-CM | **Diagnosis** |
| **046.1** | Creutzfeldt-Jakob Disease |
| **046.3** | Progressive Multifocal Leukoencephalopathy |
| **290.0** | Senile Dementia, Uncomplicated |
| **290.10** | Presenile Dementia, Uncomplicated |
| **290.11** | Presenile Dementia w/ Delirium |
| **290.12** | Presenile Dementia w/ Delusional Features |
| **290.13** | Presenile Dementia w/ Depressive Features |
| **290.20** | Senile Dementia w/ Delusional Features |
| **290.21** | Senile Dementia w/ Depressive Features |
| **290.3** | Senile Dementia w/ Delirium |
| **290.40** | Arteriosclerotic Dementia, Uncomplicated |
| **290.41** | Arteriosclerotic Dementia w/ Delirium |
| **290.42** | Arteriosclerotic Dementia w/ Delusional Features |
| **290.43** | Arteriosclerotic Dementia w/ Depressive Features |
| **291.2** | Other alcoholic dementia |
| **292.82** | Drug-induced persisting dementia |
| **294.10** | Dementia in conditions classified elsewhere without behavioral disturbance |
| **294.11** | Dementia in conditions classified elsewhere with behavioral disturbance |
| **294.8** | Other Spec Organic Brain Syndromes (Chronic) |
| **294.9** | Unspec Organic Brain Syndrome (Chronic) |
| **331.0** | Alzheimer's Disease |
| **331.11** | Pick's Disease |
| **331.19** | Other Frontotemporal Dementias |
| **331.2** | Senile Degeneration of Brain |
| **331.7** | Cerebral Degeneration in Diseases Classified Elsewhere |
| **331.82** | Dementia with Lewy Bodies |

| | |
|---|---|
| **331.89** | Other Cerebral Degeneration |
| **331.9** | Cerebral Degeneration, Unspec |

# MANUSCRIPT 3

## Use of statins and risk of dementia in heart failure

**Abstract**

**Objective:** Heart failure (HF) is associated with increased risk of dementia and dementia is an independent predictor of hospitalization in HF patients. Studies show dyslipidemia may be involved in the pathogenesis of dementia. However, it is unclear whether statins are associated with risk of dementia in HF patients. The present study examines the effectiveness of statins to prevent dementia in HF patients.

**Methods:** This retrospective, longitudinal study used a cohort of patients with HF identified from a local Medicare advantage prescription drug plan to examine incidence of dementia with up to 3 years of follow up period. Multivariable time dependent Cox model and inverse-probability-of-treatment weighting (IPTW) of marginal structural model were used to estimate the risk of developing dementia controlling for sociodemographic factors, comorbidities, comedications, appropriate laboratory measures, and potential time-varying confounding affected by previous treatment (hospitalization and low density lipoprotein test). Adjusted dementia rate ratios were estimated among current and former statin users, as compared with nonusers.

**Results:** The study included a total of 8062 HF patients (mean age 74.47 ±9.21 years) of which 1135 (14.08 %) patients were diagnosed with dementia during the median follow up of 22 months. Using the time dependent Cox model, the adjusted dementia rate ratios (95% confidence interval) among current and former users were 0.93 (0.71 to 1.21) and 0.99 (0.79 to 1.25). Use of IPTW resulted in similar findings with rate ratios (95% conservative confidence interval) of 1.24 (0.89 to 1.72) among current users and 0.94 (0.67 to 1.31) for former users as compared with the nonusers.

**Conclusion:** This study found no difference in risk of dementia among the current and former users of statin as compared with the nonusers in an already at-risk HF population.

## Introduction

Heart failure and Dementia are common medical conditions in older adults.[1] More than 5.5 million adults have heart failure (HF) in the United States (US) and the incidence approaches 10 per 1000 population after 65 years of age.[2] Despite a decline in cardiovascular mortality in developed countries over the last three decades, the burden of heart failure (HF) has risen.[3, 4] Dementia is an independent predictor of increased hospitalization in HF patients. [5, 6] One in six individuals older than 70 have dementia with prevalence increasing exponentially with advanced age. It is estimated that the number of dementia cases in 2050 will increase threefold compared with the year 2000.[9] Alzheimer's Disease (AD) is the most common followed by vascular dementia (VaD) and other forms of dementia. There is considerable overlap emerging in the risk factors and pathogenesis of vascular dementia and Alzheimer's disease.[10]

There is increasing evidence that dyslipidemia may be involved in the pathogenesis of dementia (AD and VaD).[28-36] Therefore, statins, a class of drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase [37, 38] might reduce the risk of dementia by lowering cholesterol. Statins have been shown to have an inhibiting effect on β-amyloid that triggers progression to Alzheimer's disease.[39, 40] Besides lipid lowering ability, statins also have pleiotrophic effects. These include endothelial protection by increasing nitric oxide, as well as antioxidant, anti-inflammatory, and antithrombotic effects. [35, 41] They may also reduce cellular death. [42] These effects implicate the ability of statins to act via cholesterol independent signaling pathways.[43] However, there is a mixed body of evidence as to whether statins reduce the risk of dementia.[44-46] Some evidence suggests a favorable effect of statins on cognition[47-50] while other studies have failed to show beneficial effects on cognitive function.[51-55]

To our knowledge there is no study in HF patients that assessed the effect of statins on time to dementia diagnosis. Moreover, literature showed that drug therapies have different effect on cognitive impairment in patients with and without HF.[27, 111] and dementia significantly increased the risk of hospitalization in HF patients.[5, 7, 8] Given the significant clinical impact of dementia associated with HF and the current urgency for effective treatments to reduce the incidence of dementia, the present study examines the effectiveness of statins that are widely prescribed in HF patients.

The key challenge in comparison of true treatment (causal) effects in an observational study is the presence of confounding, especially confounding by indication for treatment. Furthermore, in longitudinal studies involving chronic illnesses such as HF, some confounders change with time during the follow-up. A model that allows incorporation of time-varying variables is the extended Cox model. However, it has been argued that these models are not sufficient to give causal effect estimates in presence of time-dependent confounders that are affected by previous treatment.[72, 87] To estimate the causal effect of treatment on outcome in the presence of such confounding, marginal structural models (MSM) have been proposed.[88] In the present study, we have considered occurrence of hospitalization and low density lipoprotein (LDL-C) test to be time-dependent confounders affected by previous treatment. Physicians may adjust statin therapy after occurrence of a hospitalization or a LDL-C test that may be indicative of decompensation in overall health that could herald increased risk of dementia. However, (prior) statin therapy should benefit patients and reduce their risk of hospitalization and LDL-C levels and hence, reduce monitoring LDL-C. Therefore, hospitalization and LDL-C may be time dependent confounders affected by previous treatment in this study, because these are predictors of subsequent treatment, predicted by previous treatment, and may be associated with risk of dementia. This relationship is illustrated in the figure 1.

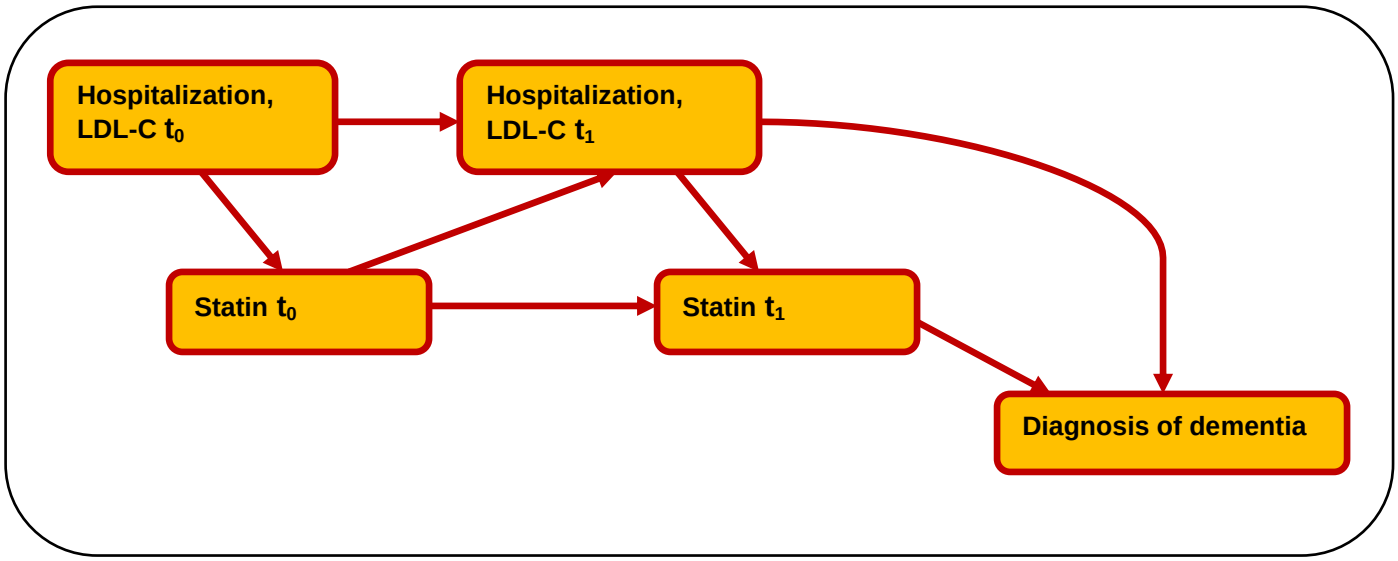



**Figure 1.** Illustration of time-dependent confounding of statin use and risk of dementia by hospitalization and low density lipoprotein (LDL-C)

The goal of this study is to test the causal effect of statin on reducing dementia in patients with heart failure using extended Cox model and Marginal structural model to account for time-dependent confounding by hospitalization and LDL-C.

## Methods

*Data source*

The study design was a retrospective longitudinal cohort of all HF patients in a Medicare Advantage Prescription Drug (MAPD) plan in Texas from January 1, 2008, to December 31, 2011. Several computerized data files including membership file, member summary file, institutional claims file, professional claims file, quest lab, CCMS and pharmacy file were used. Membership and member summary files include demographic, severity scores and cost data for beneficiaries for each year. Institutional claims include information on all inpatient claims. The files contain diagnostic information in the form of International Classification of Diseases, Ninth

Revision (ICD-9) codes, and procedure information in form of Current Procedural Terminology (CPT) codes. Professional claims contain information on all outpatient encounters. The files contain diagnostic information in the form of ICD-9-CM codes and procedure information in form of CPT codes. Quest lab files contain 153 applicable lab tests that include low-density lipoprotein (LDL-C), hemoglobin A1c (HbA1c) and creatinine. CCMS file include the hospitalization records, date of admission, date of discharge and length of stay. Pharmacy files contain Part D pharmacy data provided by pharmacy benefits manager. The pharmacy records include patient and drug identifying information, fill dates, days of supply, quantity dispensed and dosing information for each prescription filled.

*Selection of patients*

Patients were included in the study sample if they had at least one claim after the index date and diagnosed with HF (ICD-9-CM 402.01, 402.11, 402.91, 415.0X, 416.9X, 425.4X-425.9X, 428.XX, 429.4X, 785.51) between January 1, 2008, to December 31, 2011. Patients were excluded if they were diagnosed with dementia or died before the index date. Index date was defined as January 1, 2009 for patients that had HF diagnosis on or before January 1, 2009 and their coverage prior to January 1, 2008; date of HF diagnosis for patients that had 1 or more years of records prior to HF diagnosis or date at which the HF patients had at least 1 year prior records. Finally, records with missing values except for the laboratory measures were deleted from the final sample, as suggested by Little and Rubin (1989).[79]

Outcome measure

Time to dementia diagnosis. Dementia was defined based on the occurrence of any relevant ICD-9-CM codes in the inpatient or outpatient records from the index date. The diagnosis of dementia was examined through December 31, 2011. ICD-9 codes to identify dementia diagnosis are given in Appendix A.[18, 19]

Exposure

A patient's exposure to statins was assessed for the study period (01/01/2009 -12/31/2011). Exposure was classified on a monthly basis by assessment of the days' supply of the filled prescription until the termination of days' supply and the fill date of the next filled prescription occurs. Every person-month during study follow-up was classified according to use of statins. Current use was defined as use during the month when the prescription for statins covered 15 or more days. Former use was defined as use during the months after the current use or when prescription for statins covered less than 15 days. Non use was defined as no prescribed use of statins or prescription covered less than 15 days in the month being classified or any preceding months. Former users and nonusers could become current users of statins during follow-up. Exposure to statins was therefore time-varying or time-dependent, and could change over the course of follow-up.

Average daily dose (ADD) and dose category. ADD was calculated at the baseline as the total quantity of statins divided by the available days of statin therapy during the 6-month pre-index period. Dose was standardized to 40 mg of simavastatin equivalent. After calculating ADD for each patient, statin dose category was dichotomised into low dose (<40 mg simvastatin or equivalent /day) and high dose (40 mg simvastatin or more or equivalent / day).[112]

Covariates

The variation in survival rates may be associated with the time independent socio-demographic factors, treatment factors and clinical factors, therefore the study included 43 such covariates. Socio-demographic factors included age and gender. Treatment factors included various co-medications taken 1 year prior to the index date. We included diuretics (thiazide diuretics, potassium sparing diuretics and loop diuretics), digitalis glycosides, angiotensin-converting enzyme inhibitors/ angiotensin receptor blockers(ACEIs/ARBs), calcium channel blockers

(CCBs), beta blockers (BBs), vasodilators, anti arrythmics, alpha blockers, insulin, oral hypoglycemics and non statin lipotropics. Clinical factors included 22 co-morbid conditions [70, 71, 80, 81] and appropriate laboratory measures like serum creatinine, low-density lipoprotein (LDL-C), hemoglobin A1c (HbA1c). Severity of illness could not be assessed by ejection fraction (EF) or New York Heart Association (NYHA) HF classification due to lack of information in the database. Instead we used number of years in the cohort and prior hospitalization as a substitute for HF severity[70, 71]. We also included number of all drugs taken, number of co-morbid conditions and Centers for Medicare and Medicaid Services (CMS) risk score to account for medication burden and disease severity. The CMS risk score is calculated based on data taken from a large pool of beneficiaries to estimate the average predicted costs for each of the component factors (e.g., age-sex, low income status, individual disease groups). It consists of 189 disease classifications for use in risk adjusting of clinical outcomes in Medicare populations.[18, 19]

In addition to the time independent covariates, the time dependent covariates considered for the study were concurrent hospitalization, LDL-C monitoring, cumulative duration of statin use and adherence defined on a monthly basis. A patient was considered hospitalized in a particular month if she was admitted to the hospital in that month. If the length of stay in hospital was more than 30 days, then the patient was considered hospitalized for two consecutive months and so on. A patient was considered monitored for LDL-C in a particular month if she had records either in the claims or quest lab files for that month. Duration of use was calculated as cumulative duration of use by summing the duration of all prescriptions and updated monthly. Adherence-as medication possession ratio (MPR) was calculated as follows:

MPR= (Total months supply) / time available)*100.

A dichotomous variable was created as less than 80% MPR and greater than or equal to 80%MPR. [81] on monthly basis.

*Statistical analysis*

Analyses were performed using SAS software version 9.3 (SAS Institute, Cary, NC). Bivariate associations between the predictor variables and outcomes were tested using the chi-square test for categorical variables and the t test for continuous variables. Two different approaches were used to test the effect of statin use on the risk of the dementia diagnosis. First a time dependent Cox model was developed and second a marginal structural Cox model using inverse-probability-weights was constructed.

Time-dependent Cox model

Crude dementia rates for baseline statin use versus nonuse were compared. Kaplan–Meier method was used to estimate unadjusted dementia diagnosis by baseline use of statins, and the log-rank test was used to compare the groups. Next a multivariable time-dependent Cox model of time to dementia diagnosis was constructed. The independent variables used in the Cox regression were 44 time-independent factors like socio-demographic factors, treatment factors and clinical factors. And time dependent factors updated monthly like current use, former use, nonuse, duration of use, medication possession ratio and hospitalization. Patients were censored if they did not reach the outcome till December 31, 2011 (end of the study) or if the patient died before dementia diagnosis. Hazards ratios (HR) were obtained from the model after adjusting for the covariates mentioned above. Hospitalization and LDL-C test may be time dependent confounders in the present study. These are intermediate variables affected by previous treatment and predicting future treatment and also independent risk factors for dementia. Thus, simply adding these variables in the time-dependent Cox model may introduce bias and cannot provide causal effect of statin use on dementia.[72, 87]

Marginal structural Cox model

Marginal structural Cox model using inverse-probability-treatment-weights (IPTW) were used to estimate the causal effect of statin use (current use and former use) versus nonuse on dementia diagnosis. In IPTW a pseudopopulation is created that consists of “copies” of original subjects who account not only for themselves but for subjects with similar characteristics who received the other exposure.[90] In time independent exposure IPTW creates a pseudopopulation in which all subjects are considered conditionally exchangeable by achieving a balance between the treated and non-treated groups on the baseline covariables at the start of the study.[70, 71] Whereas in longitudinal studies with time varying exposure , the marginal structural models (MSMs) use the IPTW that is updated at various time points to achieve the balance between the groups not only at baseline but also at different time points. Therefore MSM allows controlling for effects of time-dependent confounders that predict the subsequent treatment and that are predicted by previous treatment.[91]

The MSM using IPTW is related to propensity scoring, where the probability that the subject received his own observed treatment, given covariables.[73, 92, 93] The IPTW is the inverse of the propensity scores that are calculated using multinomial logistic regression in case of multiple treatment settings (current users, former users and control).[70, 71]

If the propensity score distribution has large variability (possibly because some covariates are highly correlated with treatment) then the treatment patterns will have extremely large weights[91] Robins et al.[88] and Hernán et al. [94] recommend replacing the IPTW with stabilized weights to reduce this variability and ensure the estimated treatment effect remains unbiased.[91] These stabilized weights were calculated using two components, the treatment history weights and the censoring history weights.[94, 95]

Thus, in MSM, using stabilized weights, the first step was to create the treatment history weights at various time intervals. Treatment history weights for each month were calculated as conditional probability of receiving the observed treatment based on the treatment history (treatment in prior month, duration of use and adherence) and the baseline covariates divided by conditional probability of receiving the observed treatment based on the treatment history and the baseline covariates and also the time dependent covariates (hospitalization, LDL-C test, prior month hospitalization, prior month LDL-C test).[72, 94] The second step was to calculate the censoring history weight to adjust for censoring by mortality or end of the study. The censoring history weights were calculated by similar procedure as treatment history weights. Next the above two calculated weights were multiplied to create stabilized weights for each subject in each time period.[95] The final step was to estimate the probability of having observed outcome, dementia diagnosis, among those with observed treatment histories, a weighted pooled logistic regression model was estimated, treating each person-month as an observation. The model was also controlled for all baseline covariates. Under the assumptions of positivity, consistency, no model misspecification, and no unmeasured confounding, the treatment effects in this model can be interpreted as causal effects.[72] To correct the correlation between subjects arising due to repeated measures taken on the same individual, we used generalizing estimating equations with robust standard errors from an independent working correlation matrix to fit the weighted pooled logistic regression model.The estimates obtained from MSM were compared with the hazards ratio obtained from time-dependent Cox model to determine the bias due to presence of time-varying confounding factors (hospitalization and LDL-C test).

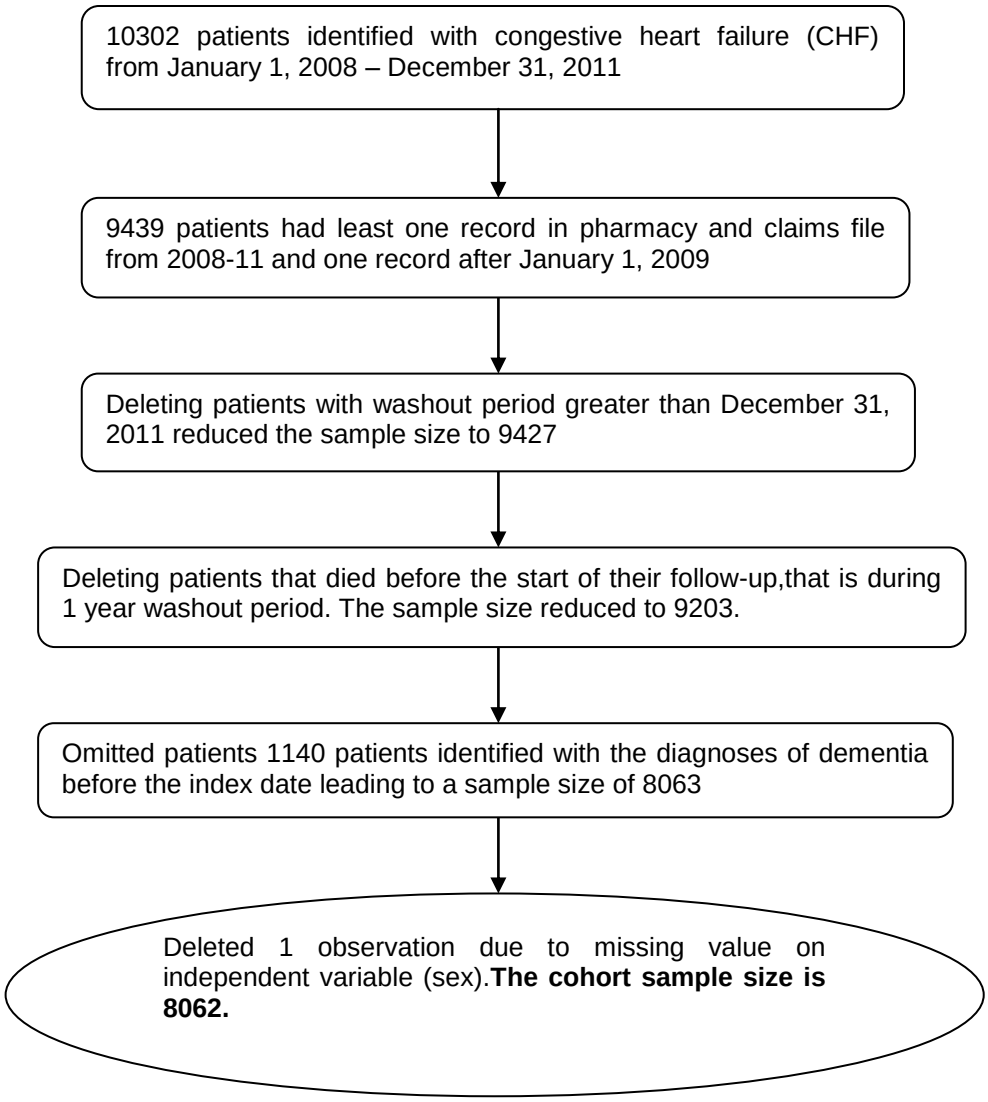
Sub-group analysis

Two separate subgroup analysis were carried out that restricted the age group to >= 65-years and that used a new user design for drug exposure.[96] The study was approved by the Institutional Review Board of University of Houston.

## Results

The process of selection of patients for the analysis is outlined in the Fig. 2. A total of 8063 patients with HF were identified that met inclusion and exclusion criteria. There was one record with missing data on gender and was excluded from analysis. Thus, the study sample comprised 8062 HF patients of which 1135 (14.08 %) patients were diagnosed with dementia over a follow up to 36 months period between January 01, 2009 and December 31, 2011. The median length of follow-up for the cohort was 22 months for a total follow-up of 180 381 patient months.

**Figure 2** Derivation of the study sample.

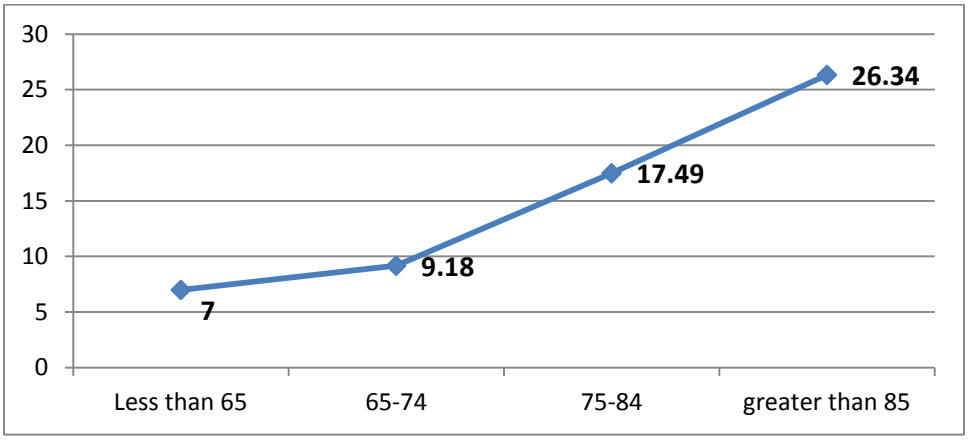



Patient characteristics

Table 1 compares the baseline characteristics of patients with and without dementia. The mean age (± standard deviation) of the HF cohort was 74.47 (±9.21) years. Patients with dementia were older (78.23 ± 8.53 years) than those without dementia (73.85 ± 9.17 years, *P* < .0001). The incidence of dementia increased with age from 7.00% in the < 65 -year age group to 9.18%

in the 65-74, to 17.49% in the 75-84 and to 26.34% in the >85-year age groups (Figure 3). Sex was not associated with a diagnosis of dementia. (*P* =0.199).

**Figure 3.** Incidence of dementia among different age-groups




About 39% patients had more than 5 co-morbid conditions. Of the 22 co-morbid conditions, top five co-morbid conditions were hypertension (87.14%), hyperlipidemia (60.33%), ischemic heart disease (46.81%), diabetes (45.19%) and chronic lung disease (37.35%). Hypertension (87.31% vs 87.11%, *P*= 0.849), diabetes (47.31% vs 44.48%, *P*= 0.121) and chronic lung disease (37.53% vs 37.32%, *P*=0.890) had similar percent of patients with and without dementia, but the two groups differed significantly on hyperlipidemia (52.16% vs 61.67%, *P* <.0001*)* and Ischemic heart disease (49.96% vs 46.30%, *P*= 0.022*)*. Approximately 22% of the patients had prior hospitalization, which was significantly associated with dementia (*P*<.0001). Increasing years with HF and higher comorbid conditions were each associated with a higher incidence of dementia (*P*< .0001), however no statistical significance was noted with CMS risk score in regards to diagnosis of dementia (*P*= 0.236).

In unadjusted analysis, patients taking CCBs (*P*=0.0001) and alpha-blockers (*P*= 0.006) had a higher incidence of dementia. The ADD for baseline use of statin (simvastain equivalent) was

37.95 (±30.02) mg and 48.29% (n=1825) patients received high dose statin (40 mg simvastatin or more or equivalent / day) among the baseline statin users (n=3779).

**Table 1.** CHF Patient Characteristics -8062 patients

| | Total N(%) | Dementia N(%) | No Dementia N (%) | *p-value* |
|---|---|---|---|---|
| **Patient count** | 8062(100) | 1135(14.08) | 6927(85.92) | |
| **Age in years** mean (SD) | 74.47(9.21) | 78.23(8.53) | 73.85(9.17) | <.0001* |
| **Age groups** | | | | |
| < 65 | 929 (11.52) | 65(5.73) | 864(12.47) | <.0001* |
| 65-74 | 3128(38.80) | 287(25.29) | 2841(41.01) | |
| 75-84 | 3071(38.09) | 537(47.31) | 2534(36.58) | |
| >=85 | 934(11.59) | 246(21.67) | 688(9.93) | |
| **Gender** | | | | |
| Males | 3786(46.96) | 513(45.20) | 3273(47.25) | 0.199 |
| Females | 4276(53.04) | 622(54.80) | 3654(52.75) | |
| **CMS Risk Scores** mean (SD) | 1.60(1.12) | 1.58(1.08) | 1.62(1.20) | 0.236 |
| **Co-morbidities** | | | | |
| Hypertension | 7025(87.14) | 991(87.31) | 6034(87.11) | 0.8488 |
| Ischemic Heart Disease | 3774(46.81) | 567(49.96) | 3207(46.30) | 0.022* |
| Conduction Disorders | 1334(16.55) | 196(17.27) | 1138(16.43) | 0.480 |
| Cardiac Arrhythmias | 1960(24.31) | 304(26.78) | 1656(23.91) | 0.036* |
| Valvular Heart Disease | 1776(22.03) | 271(23.88) | 1505(21.73) | 0.105 |
| Cerebrovascular Disease | 1286(15.95) | 254(22.38) | 1032(14.90) | <0.0001* |
| Chronic lung disease | 3011(37.35) | 426(37.53) | 2585(37.32) | 0.890 |
| Diabetes | 3643(45.19) | 537(47.31) | 3106(44.84) | 0.1206 |
| Renal disease/Renal Failure | 2234(27.71) | 359(31.63) | 1875(27.07) | 0.001* |
| Disorders of upper GI and Liver | 689(8.55) | 106(9.34) | 583(8.42) | 0.303 |
| Non-Skin Malignancies | 822(10.20) | 124(10.93) | 698(10.08) | 0.381 |
| Anemia & Coagulation Disorders | 1804(22.38) | 290(25.55) | 1514(21.86) | 0.006* |
| Decubitus and LE ulcers | 428(5.31) | 86(7.58) | 342(4.94) | 0.0002* |
| HIV | 6(0.07) | 1(0.09) | 5(0.07) | 0.855 |
| Thyroid Disorders | 1395(17.30) | 217(19.12) | 1178(17.01) | 0.081* |
| Sleep Apnea | 362(4.49) | 42(3.70) | 320(4.62) | 0.166 |
| Alcohol Related Disease | 82(1.02) | 6(0.53) | 76(1.10) | 0.077* |
| Other Psychiatric Disorders | 1300(16.13) | 242(21.32) | 1058(15.27) | <0.0001* |
| Pulmonary Heart Disease | 431(5.35) | 64(5.64) | 367(5.30) | 0.636 |
| Thromboembolism | 448(5.56) | 70(6.17) | 378(5.46) | 0.333 |
| Hyperlipidemia | 4864(60.33) | 592(52.16) | 4272(61.67) | <.0001* |
| Peripheral arterial disease | 1730(21.46) | 296(26.08) | 1434(20.70) | <0.0001* |
| **Prior hospitalization** | 3379(41.91) | 572(50.40) | 2807(40.52) | <.0001* |
| **Number of co-morbid conditions** | | | | |
| Less than or equal to 5 | 4935(61.21) | 635(55.95) | 4300(62.08) | <.0001* |
| More than 5 | 3127(38.79) | 500(44.05) | 2627(37.92) | |
| **Years with HF** | | | | |

| | Total N(%) | Dementia N(%) | No Dementia N (%) | *p-value* |
|---|---|---|---|---|
| 0 | 3923(48.66) | 420(37.00) | 3503(50.57) | <.0001* |
| 1 | 1677(20.80) | 233(20.53) | 1444(20.85) | |
| 2 | 1164(14.44) | 210(18.50) | 954(13.77) | |
| =>3 | 1298(16.10) | 272(23.96) | 1026(14.81) | |
| **Co-medications** | | | | |
| Beta Blocker Use | 4478(55.54) | 633(55.77) | 3845(55.51) | 0.869 |
| CCB Use | 2708(33.59) | 438(38.59) | 2270(32.77) | 0.0001* |
| Digoxin Use | 813(10.08) | 140(12.33) | 673(9.72) | 0.007* |
| Anti Anginals Use | 38(0.47) | 3(0.26) | 35(0.51) | 0.272 |
| Vasodilators Use | 1526(18.93) | 233(20.53) | 1293(18.67) | 0.138 |
| Diuretics Use | 5044(62.57) | 713(2.82) | 4331(62.52) | 0.849 |
| Alpha blockers use | 388(4.81) | 73(6.43) | 315(4.55) | 0.006* |
| Anti Arrythmic use | 422(5.23) | 67(5.90) | 355(5.12) | 0.275 |
| Insulin use | 1137(14.10) | 179(15.77) | 958(13.83) | 0.082 |
| Hypoglycemic use | 2475(30.70) | 358(31.54) | 2117(0.56) | 0.507 |
| Non- statin lipotropic use | 1242(15.41) | 154(13.57) | 1088(15.71) | 0.064 |
| Statins at baseline (6 months) | 3779 (46.87) | 512(45.11) | 3267(47.16) | 0.200 |
| ACEI/ARB use | 4249(52.70) | 708(62.38) | 4480(64.67) | 0.135 |
| **Number of drugs** | | | | |
| Less than or equal to 3 | 3737(46.35) | 529(46.61) | 3208(46.31) | 0.853 |
| More than 3 | 4325(53.65) | 606(53.39) | 3719(53.69) | |
| **Serum creatinine level** | | | | |
| <1.5 | 4484(55.62) | 628(55.33) | 3856(55.67) | <.0001* |
| 1.5-2.5 | 723(8.97) | 137(12.07) | 586(8.46) | |
| >2.5 | 179(2.22) | 33(2.91) | 146(2.11) | |
| Unknown | 2676(33.19) | 337(29.69) | 2339(33.77) | |
| **Hemoglobin A1-c** | | | | |
| <=7 | 1859(23.06) | 282(24.85) | 1577(22.77) | 0.003* |
| >7 | 849(10.53) | 145(12.78) | 704(10.16) | |
| Unknown | 5354(66.41) | 708(62.38) | 4646(67.07) | |
| **Low-density lipoprotein** | | | | |
| <100 | 2692(33.39) | 428(37.71) | 2264(32.68) | 0.001* |
| 100-129 | 1073(13.31) | 144(12.69) | 929(13.41) | |
| >129 | 650(8.06) | 81(7.14) | 569(8.21) | |
| Unknown | 3647(45.24) | 482(42.47) | 3156(45.69) | |

* indicates statistically significant difference

LE, lupus erythematosus; HF, heart failure; CCB, calcium channel blocker; ACEI, angiotensin-converting enzyme inhibitors;ARB, angiotensin receptor blockers

Time-dependent Cox model

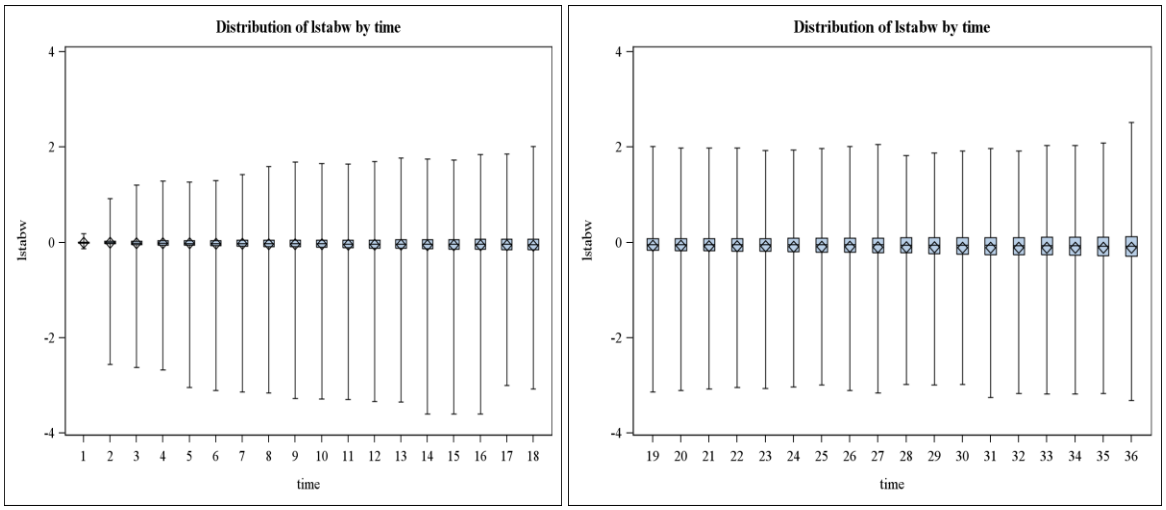
There were no significant differences in the crude dementia rates for baseline users of statin (13.55%) vs nonusers (14.55%) (*P*= 0.200). The Kaplan Meier curve showed that unadjusted

survival was similar across baseline statin users vs nonusers (*P*=0.094 for log rank test). Multivariable time-dependent Cox model found that as compared to the nonusers, the adjusted hazards ratio did not differ significantly among the current users of statin (HR, 0.93; 95% confidence interval [CI], 0.71 to 1.21) or among former users (HR, 0.99; 95% CI, 0.79 to 1.25) (Table 2).

Marginal structural Cox model

Figure 3 presents the distribution of the final weights, which combine information on statin and censoring history, for the follow-up times (a logarithmic transformation was applied for display purposes only). The distribution of stabilized weights was symmetric and centered around 1 at all times (mean = 1.009, SD = 0.39).

**Figure 3.** Distribution of stabilized weights




After adjusting for the time-dependent confounders (hospitalization and LDL-C) in addition to the other confounders (listed in table 1) and applying stabilized weights to a pooled logistic regression, the estimated causal dementia rate ratio was 1.24 (95% conservative confidence interval-0.89 to 1.72) for current users and 0.94 (95% conservative confidence interval-0.67 to

1.31) for former users. Thus under our assumptions of positivity, consistency, no model misspecification, and no unmeasured confounding, statin current use or former use does not appear to decrease the risk of dementia.(Table 2) These estimates were similar to the hazards ratio obtained from the standard time-dependent Cox model in terms of no statistical significance.

Sub-group analysis

We performed two sub-group analyses to test the robustness of study findings (Table 2). To assess for the possible bias from inclusion of subjects <65-years of age and disabled, we restricted our analysis to all persons 65 years of age or older. Findings were essentially identical to those of the primary analysis for both time dependent Cox model (Current users, HR, 0.88; 95% CI, 0.67 to 1.16; former users, HR, 0.98; 95% CI, 0.77 to 1.23) and marginal structural Cox model (Current users, HR, 1.22; 95% CI, 0.86 to 1.74; former users, HR, 0.92; 95% CI, 0.64 to 1.31). In the analyses that included only the new users (defined as no use of ACEI/ARB during the 6 months prior to the index date), we found no association between ACEI/ARB use ( current and former) and risk of dementia.

**Table 2.** Adjusted rate ratio, 95% Confidence interval and p-value for time-dependent Cox model and IPTW estimation of marginal structural Cox model

| Effect | Rate Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| **Primary Analysis for all subjects in HF cohort** | | | |
| Time-dependent Cox model | | | |
| Current users vs nonusers | 0.93 | 0.71- 1.21 | 0.590 |
| Former users vs nonusers | 0.99 | 0.79- 1.25 | 0.957 |
| IPTW estimation of marginal structural Cox model | | | |
| Current users vs nonusers | 1.24 | 0.89- 1.72 | 0.195 |
| Former users vs nonusers | 0.94 | 0.67- 1.31 | 0.713 |
| **Analysis restricted to subjects 65 years of age or older** | | | |
| Time-dependent Cox model | | | |
| Current users vs nonusers | 0.88 | 0.67- 1.16 | 0.350 |
| Former users vs nonusers | 0.98 | 0.77- 1.23 | 0.808 |
| IPTW estimation of marginal structural Cox model | | | |
| Current users vs nonusers | 1.22 | 0.86- 1.74 | 0.248 |

| Effect | Rate Ratio | 95% Confidence Interval | p-value |
|---|---|---|---|
| Former users vs nonusers | 0.92 | 0.64- 1.31 | 0.628 |
| **Analysis restricted to new users of statin** | | | |
| Time-dependent Cox model | | | |
| Current users vs nonusers | 0.92 | 0.60-1.41 | 0.687 |
| Former users vs nonusers | 1.06 | 0.77- 1.45 | 0.723 |
| IPTW estimation of marginal structural Cox model | | | |
| Current users vs nonusers | 1.16 | 0.80- 1.69 | 0.431 |
| Former users vs nonusers | 1.01 | 0.68- 1.50 | 0.957 |

## Discussion

This study tested the hypothesis that statin would reduce the risk of dementia in patients with HF. These results demonstrate that with the current or former use of stains there was no significant difference in the risk of dementia as compared with the nonuse. Unbiased estimation of the effect of treatment in an observational study requires adjustment for time-dependent confounding.[97] Standard time-dependent Cox model that incorporate time varying variables give biased estimates of the true effect of treatment in presence of these time varying confounders. Therefore, to estimate the causal effect of statin on risk of dementia we used both a time-dependent Cox model and IPTW estimation of a marginal structural Cox model. The findings from the standard Cox model were similar to that of the MSM, indicating that the mediation by the time varying confounders (hospitalization and LDL-C) considered in the study was not significant.

We performed sub group analyses to test the robustness of our findings. We restricted our analysis to all persons 65 years of age or older to assess for the possible bias from inclusion of subjects <65-years of age and disabled. We also performed an analysis restricted to new users to address bias that would be introduced from the inclusion of prevalent users in the cohort.[96] The results from the sub group analyses were essentially identical to those of the primary analysis.

To the best of our knowledge, this is the first study to examine the effect of statin use on risk of dementia in HF patients. Many non-randomized studies have suggested benefits of statins in patients with HF and a number of prospective studies in ischemic and nonischemic HF have shown favorable effects on left ventricular function and clinical status.[56-62] Recently the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA)[63] and the Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza cardiaca (GISSI) trials[64] demonstrated that statins are safe in patients with heart failure. The European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of HF 2008 suggests consideration of the use of statins in elderly patients with symptomatic chronic HF and systolic dysfunction caused by coronary artery disease to reduce cardiovascular hospitalization.[65, 66]

The literature on effect of statin use on risk of dementia in population without HF is mixed. Some prior studies have shown a statistically significant decrease in risk of AD and other dementia among persons receiving statin therapy. A longitudinal, observational study conducted on 3069 cognitively healthy elderly patients (≥75 years of age) enrolled in the Ginkgo Evaluation of Memory Study found, the current use of statins was consistently associated with a reduced risk of all-cause dementia (hazard ratio [HR], 0.79; 95% CI, 0.65-0.96) and AD (HR, 0.57; 95% CI, 0.39-0.85).[66] In a population-based Rotterdam Study Haag et al. reported that compared with never use of cholesterol-lowering drugs, statin use was associated with a decreased risk of AD with a mean follow-up of 9 years period. Carlsson et al. in a 4-month randomized, double-blind, controlled trail evaluated the effects of simvastatin 40 mg daily vs. placebo on cognition and found that simvastatin use improved selected measures of cognitive function. Also, our prior work in the Medicare-merged veterans sample with diabetes found a protective association of statin use and time to dementia diagnosis, with hazard ratio 0.86 (95% CI, 0.83, 0.89).[75]

In contrast other studies have failed to show a lower risk of AD and dementia with statin use. A randomized, double-blind, placebo-controlled trial of simvastatin conducted in individuals with mild to moderate AD and normal lipid levels, found no benefit on the progression of symptoms in AD with use of statin.[113] Similarly, other randomized controlled trials like the Medical Research Council/ British Heart Foundation Heart Protection Study (HPS) and a prospective study of pravastatin in the elderly at risk (PROSPER), demonstrated no significant effect on cognitive function with use of statins.[37] In the Cache county study, Zandi et al.[53] found that neither the statin use at baseline nor at follow up predicted incidence of dementia or AD. Our study showed similar findings. However, none of the aforementioned studies was done to assess the effects of statin use on an already-at-risk HF population.

A possible explanation for our findings is that follow-up period was relatively short with median length of follow-up of 22 months to observe incident dementia. However this study found significant increases in dementia rates as age increased, thus giving face validity to the study results (Figure 3).[18] Another reason could be confounding by severity of illness, as we could not account for information on ejection fraction and NYHA HF classification. However, we attempted to control for this by adjusting for the number *of* years with HF, number of all medicine, and prior hospitalization of the patients, as in other large studies of HF patients.[70, 71, 80] We also adjusted for 21 co-morbidities, CMS risk scores and accounted for time-dependent confounding by indication by adding monthly hospitalization and LDL-C test records as a severity of illness factor in MSM. Finally, our findings provide a cross-sectional view of real clinical practice in a cohort of HF patients with a follow up to 3 years for a long term condition.

Our study possesses several unique strengths. Our cohort, with a high prevalence of comorbidities and abundantly prescribed comedications, adequately represents the patient

population in real‐world practice settings. Our study uses some important clinical factors like the serum creatinine, HbA1c and LDL-C values that are not usually recorded in retrospective databases. Use of dose information of the statins strengthens the results as it plays an important role in predicting the clinical outcomes in HF patients.[114] We addressed the issue of non‐randomized treatment allocation in an observational study by creating a pseudo‐randomized sample by applying inverse probability of treatment weights to the sample.[72] As time dependent Cox model cannot address the issue of time dependent confounding by indication we also carried out the analysis using MSM. Our results were robust independently of the analytical strategy and the sub group analyses performed.

The interpretation of results of this study should be made in light of several limitations. First, for MSM to have valid estimates we make an assumption of no unmeasured confounding, which remains untestable. However, It is likely that any potential unmeasured confounders would be somewhat correlated with the numerous sociodemographic, clinical and severity of illness measures that were measured, thus reducing residual confounding. However, we could not control for other potential risk factors for dementia, such as race, education, diet, smoking, and alcohol use. In addition to lacking information on disease severity (ejection fraction and NYHA HF classification), the ICD-9-CM codes used to identify HF cannot differentiate between systolic and diastolic left ventricular dysfunction. Hogg et al.[109] estimated patients with HF to be equally distributed between systolic and diastolic dysfunction, suggesting it is reasonable to consider them same and thus studying effects of treatment on all HF patients.[89] Distinguishing vascular from Alzheimer-type dementia is probably not reliable in our data. Finally, dispensed prescriptions were considered as actually consumed. However, in general, pharmacy claims have been demonstrated to be an accurate measure of prescription drug consumption.[110] To

the extent possible, measures of adherence or persistence of use were created in a cumulative and time-varying manner during follow-up to strengthen analyses.

In conclusion, in absence of randomized clinical trials, appropriate adjustment for time-varying confounding by indication may provide the best evidence to estimate the treatment effect in observational studies. This exploratory study using time-dependent Cox model and MSM found no association between the current or former use of statin as compared with the nonuse in a HF cohort. Further research needs to be done to compare the effects of statins in patients with and without HF.

***Appendix A***

| Dementia Diagnostic Codes | |
|---|---|
| ICD-9-CM | **Diagnosis** |
| **046.1** | Creutzfeldt-Jakob Disease |
| **046.3** | Progressive Multifocal Leukoencephalopathy |
| **290.0** | Senile Dementia, Uncomplicated |
| **290.10** | Presenile Dementia, Uncomplicated |
| **290.11** | Presenile Dementia w/ Delirium |
| **290.12** | Presenile Dementia w/ Delusional Features |
| **290.13** | Presenile Dementia w/ Depressive Features |
| **290.20** | Senile Dementia w/ Delusional Features |
| **290.21** | Senile Dementia w/ Depressive Features |
| **290.3** | Senile Dementia w/ Delirium |
| **290.40** | Arteriosclerotic Dementia, Uncomplicated |
| **290.41** | Arteriosclerotic Dementia w/ Delirium |
| **290.42** | Arteriosclerotic Dementia w/ Delusional Features |
| **290.43** | Arteriosclerotic Dementia w/ Depressive Features |
| **291.2** | Other alcoholic dementia |
| **292.82** | Drug-induced persisting dementia |
| **294.10** | Dementia in conditions classified elsewhere without behavioral disturbance |
| **294.11** | Dementia in conditions classified elsewhere with behavioral disturbance |
| **294.8** | Other Spec Organic Brain Syndromes (Chronic) |
| **294.9** | Unspec Organic Brain Syndrome (Chronic) |
| **331.0** | Alzheimer's Disease |
| **331.11** | Pick's Disease |
| **331.19** | Other Frontotemporal Dementias |
| **331.2** | Senile Degeneration of Brain |
| **331.7** | Cerebral Degeneration in Diseases Classified Elsewhere |

| | |
|---|---|
| **331.82** | Dementia with Lewy Bodies |
| **331.89** | Other Cerebral Degeneration |
| **331.9** | Cerebral Degeneration, Unspec |

# SUMMARY OF FINDINGS

## Specific Aim1

| Factors that significantly predict the use of ACEIs/ARBs | Factors that significantly predict the use of statins |
|---|---|
| 1. Sex<br>2. Age<br>3. Years with heart failure<br>4. Co-medications used<br>vasodilators<br>oral hypoglycemics<br>5. Co-morbidities<br>hypertension.<br>valvular heart disease<br>chronic lung disease<br>anemia & coagulation disorders<br>decubitus and LE ulcers<br>thyroid disorders<br>other psychiatric disorders<br>6. CMS risk score<br>7. Number of Drugs used<br>8. Serum creatinine level | 1. Age<br>2. Years with heart failure<br>3. Co-medications used<br>diuretics<br>digoxin<br>4. Co-morbidities<br>ischemic heart disease<br>cardiac arrhythmias<br>cerebrovascular disease<br>chronic lung disease<br>anemia & coagulation disorders<br>decubitus and LE ulcers<br>sleep apnea<br>alcohol related disease<br>hyperlipidemia<br>5. Prior hospitalization<br>6. Numbers of Drugs used<br>7. Serum creatinine level<br>8. Low-density lipoprotein |

## Specific Aim2

| Association between current ACEI/ARB users and risk of dementia diagnosis using extended cox model | Association between current statin users and risk of dementia diagnosis using extended cox model |
|---|---|
| From the hazards ratios obtained, we found no difference in the risk of dementia diagnosis between the users of ACEIs/ARBs and non users. | From the hazards ratios obtained, we found no difference in the risk of dementia diagnosis between the users of statins and non users. |

## Specific Aim3

| Association between current ACEI/ARB users and risk of dementia diagnosis using MSM and comparison of estimates with Aim 2 | Association between current statin users and risk of dementia diagnosis using MSM and comparison of estimates with Aim 2 |
|---|---|
| 1. The standard statistical methods like cox-model are not appropriate when there exists time-dependent | 1. The standard statistical methods like cox-model are not appropriate when there exists time-dependent |

| Association between current ACEI/ARB users and risk of dementia diagnosis using MSM and comparison of estimates with Aim 2 | Association between current statin users and risk of dementia diagnosis using MSM and comparison of estimates with Aim 2 |
|---|---|
| confounding by variables that are affected by previous treatment.<br>2. We considered hospitalization as a time dependent confounding variable and used MSM.<br>3. The hazards rate ratios suggested no difference in the risk of dementia diagnosis between the users of ACEIs/ARBs and non users.<br>4. The estimates obtained from MSMs were not much different from the cox models. | confounding by variables that are affected by previous treatment.<br>2. We considered hospitalization and LDL-C test as a time dependent confounding variables and used MSM.<br>3. The hazards rate ratios suggested no difference in the risk of dementia diagnosis between the users of statins and non users.<br>4. The estimates obtained from MSMs were not much different from the cox models. |

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## CONCLUSIONS

This exploratory study using time-dependent Cox model and MSM found

- no association between the current or former use of ACEI/ARB and the nonuse in a HF cohort.
- no association between the current or former use of statin and the nonuse in a HF cohort.

MSM provided similar effect estimates to the time dependent Cox model indicating that the mediation by time-dependent confounder considered in the study was not significant.

Further research needs to be done in HF population in which other measures like changing blood pressure or ejection fractions could be handled as time varying confounders. It would be interesting to compare the effects of these drugs in patients with and without HF. The findings from this study adds to the empirical knowledge of effect of ACEIs/ARBs and statins on risk of dementia in patients with HF, in elderly patients in particular where less is known.

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