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Ishveen Kaur Chopra

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**IMPACT OF INCIDENT CANCER ON CORONARY ARTERY DISEASE-RELATED
CONCOMITANT MEDICATION ADHERENCE, SHORT-TERM HEALTH AND ECONOMIC
OUTCOMES AMONG ELDERLY MEDICARE BENEFICIARIES WITH CORONARY
ARTERY DISEASE**

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**Dissertation submitted to the School of Pharmacy
at West Virginia University
in partial fulfillment of the requirements
for the degree of**

**Doctor of Philosophy
in
Health Services and Outcomes Research**

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**Morgantown, West Virginia
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**Keywords: Cancer, Coronary artery disease, Concomitant medication adherence, Health outcomes,
Health expenditures
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Abstract

Impact of Incident Cancer on Coronary Artery Disease-Related Concomitant Medication Adherence, Short-Term Health and Economic Outcomes among Elderly Medicare Beneficiaries with Coronary Artery Disease

Ishveen Kaur Chopra

Coronary artery disease (CAD) is one of the most burdensome chronic conditions in the elderly. The two key goals of long-term management of CAD are (i) to reduce symptoms and ischemia and (ii) prevent myocardial infarction and death, by lowering lipids and blood pressure. Of all the risk reduction strategies, use and adherence to concomitant pharmacotherapy with statins and beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) have been shown to be highly effective and has become the cornerstone of CAD management. However, adherence to concomitant pharmacotherapy can be influenced by many factors including the development of other life-threatening conditions such as cancer. To date, no real-world study has assessed how incident cancer can affect adherence to concomitant pharmacotherapy and whether concomitant pharmacotherapy can minimize the negative effects of some cancer treatments on CAD-related morbidity and expenditures among individuals with CAD and incident cancer. To fill the knowledge gap, the three related aims of this dissertation were to analyze: 1) the association between incident breast, colorectal, and prostate cancer diagnosis and adherence to statins and/or ACEIs/ARBs/beta-blockers among elderly fee-for-service (FFS) Medicare beneficiaries with pre-existing CAD; 2) the impact of non-adherence to these medication classes on short-term CAD-related hospitalizations in patients with incident cancer diagnosis; and 3) the impact of incident cancer diagnosis on short-term CAD-related inpatient and outpatient healthcare expenditures. The study used a retrospective observational longitudinal cohort study design was conducted among elderly Medicare FFS beneficiaries with pre-existing CAD and those with incident breast cancer (BC), colorectal cancer (CC), or prostate cancer (PC), using multiple years (2005-2012). The study data was derived from the cancer registry data from Surveillance, Epidemiology and End Results (SEER) program linked with the Medicare claims data, the American community survey census-tract files and Area Health Resource Files. Aim 1 and Aim 3 also included 5% non-cancer random sample of Medicare beneficiaries, residing in SEER regions, with pre-existing CAD. Each individual was observed for 48 months with 24-month baseline (for identification of CAD and baseline characteristics) period, 12-month pre-index, and 12-month post-index periods. In the first aim, only 28.9% of the elderly with CAD were adherent to both statins and ACEIs/ARBs/beta-blockers. In the adjusted analyses, women [AOR = 0.70; 95% CI = 0.58, 0.81; $P < 0.0001$] and men [AOR = 0.63; 95% CI = 0.51, 0.75; $P < 0.0001$] with CC and men with PC [AOR = 0.92; 95% CI = 0.85, 0.99; $P = 0.022$] were significantly less likely to be adherent to both medication classes compared to women and men with NC, respectively. No significant differences in adherence to medications were observed among women with BC compared to women with NC. Even among those using single medication class, women [AOR = 0.64; 95% CI = 0.50, 0.79; $P < 0.0001$] and men with CC [AOR = 0.59; 95% CI = 0.42, 0.76; $P < 0.0001$] were significantly less likely to be adherent to that medication class compared to women and men with NC. In the second aim, adherence to both statins and ACEIs/ARBs/beta-blockers was estimated at 31.2% during the 120-day period immediately after cancer diagnosis; 13.7% were not adherent to both medication classes during the same period; 27.4% had CAD-related hospitalizations immediately after cancer diagnosis and this percentage declined to 10.6% during the last four months of the post-cancer period. In the adjusted analyses, those not adherent to both statins and ACEIs/ARBs/beta-blockers were more likely to have CAD-related hospitalization compared to those who were adherent to both medication classes [AOR = 1.82; 95% CI = 1.72, 1.92; $P < 0.0001$]. In the third aim, overall, CAD-related mean healthcare expenditures at pre-index period accounted for about 32.6% - 39.5% of total expenditures among women and 41.5% - 46.8% among men. In the adjusted GLMM, all cancer groups had significantly higher CAD-related healthcare expenditures compared to the non-cancer groups. Women with CC 153% higher expenditures compared to women with no cancer [$\beta = 0.93$, $P < 0.0001$]. Men with CC had 166% higher expenditures compared to men with NC [$\beta = 0.98$, $P < 0.0001$]. Further, men and women with CC had 57% and 55% higher expenditures compared to men with PC and women with BC, respectively. In summary, the study findings, collectively, suggest that cancer diagnosis negatively impacts adherence to CAD pharmacotherapy. Reduction in adherence was associated with increase in CAD-related hospitalizations and subsequent increase in CAD-related expenditures. This warrants the integration of cardiovascular care in the elderly diagnosed with cancer.

Future studies need to explore whether the emerging collaborative care models, such as medical homes, can reduce inpatient use, and consequently, CAD-related expenditures.

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List of Abbreviations

ACEI	Angiotensin-converting enzyme inhibitors
ADT	Androgen deprivation therapy
AHRF	Area Health Resources File
AHRQ	Agency for Healthcare Research and Quality
AOR	Adjusted odds ratio
ARB	Angiotensin II receptor blockers
AJCC	American Joint Committee on Cancer
ACS	American Community Survey
BCW	Women with breast cancer
BP	Blood pressure
BRFSS	Behavioral Risk Factor Surveillance System
CAD	Coronary artery disease
CCM	Men with colorectal cancer
CCW	Women with colorectal cancer
CDC	Centers for Disease Control and Prevention
CPT-4	Common Procedural Terminology, 4th Edition
DALY	Disability-adjusted life years
DME	Durable Medical Equipment
FFS	Fee-for-service
GEE	Generalized estimating equations
GLMM	Generalized linear mixed models
HHA	Home Health Agency
HCPCS	Health Care Procedure Classification Code
HCUP	Healthcare Cost and Utilization Project
HPSA	Health professional shortage area
HRQoL	Health-related quality of life
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-O-3	International Classification of Diseases for Oncology, 3rd Edition
LDL-C	Low-density lipoprotein cholesterol
MACRA	Medicare Access and Children's Health Insurance Program Reauthorization Act
MCC	Multiple Chronic Conditions
MEDPAR	Medicare Provider Analysis and Review
MI	Myocardial infarction
MPR	Medication Possession Ratio
NCH	National Claims History
NCM	Men with no cancer

NCW	Women with no cancer
NDC	National Drug Code
NHANES	National Health and Nutrition Examination Survey
OR	Odds ratio
PCM	Men with prostate cancer
PCP	Primary care physician
PDC	Proportion of days covered
PDE	Part D Event
PEDSF	Patient Entitlement and Diagnosis Summary File
QALY	Quality-adjusted life year
RR	Relative risk
SNF	Skilled Nursing Facility
SEER	Surveillance, Epidemiology, and End Results
SUMDENOM	Summarized Denominator
US	United States
USD	United States dollar
Wt	Weighted

CHAPTER 1

Introduction

1.1 Coronary Artery Disease

1.1.1 Epidemiology of Coronary Artery Disease

Coronary artery disease (CAD), also referred to as coronary heart disease or ischemic heart disease, is caused by atherosclerosis, is a disease in which there is narrowing or blockage of the coronary arteries, blood vessels that carry blood and oxygen to the heart [1]. Globally, CAD prevalence rate in 2006-2013 was 13.8% [2]. The Framingham study investigators estimated a lifetime risk of developing CAD at 49% in men and 32% in women [3].

In the United States (US), nearly 15.5 million adults aged 20 and older are diagnosed with CAD, [4] with prevalence rates of 6.2% [4]. In 2015, approximately 635,000 new cases of CAD were diagnosed in adults aged 20 years and older [4]. Sex and race/ethnicity differences in CAD incidence and prevalence rates were also reported [4-6]. The average age-standardized CAD incidence rates have been reported to be 9.0 per 1,000 person years for black men *versus* 8.1 for white men and 5.0 for black women *versus* 3.4 for white women [5]. Hispanics (6.1%) have higher age-adjusted prevalence of CAD as compared to whites (5.8%) [6]. Women have lower prevalence of CAD (5.0%) as compared to men (7.6%) [4]. However, it is not known as to whether this lower prevalence is due to differences in presentation of CAD leading to under-detection of CAD in women [7, 8].

1.2 Burden of CAD

1.2.1 Mortality

Although the survival rate of CAD has been steadily improving [9], it still remains the leading cause of mortality worldwide; with 7.4 million deaths in 2012, 13.2% of total global mortality [10]. It is projected that by 2020, worldwide, 11.1 million deaths will be due to CAD [11]. In the US, CAD is responsible for more than two-thirds of all heart-related mortality, with more than 380,000 deaths annually [12]. CAD claims more lives than all forms of cancer combined [4]. Mortality from CAD disproportionately affects the elderly, men, and racial minorities [4, 13, 14]. For example, 80% of CAD-related mortality is reported among elderly population (65 years and older) [4].

1.2.2 Morbidity – Complications of CAD

Worldwide, CAD is the leading cause of morbidity, with 32.4 million myocardial infarctions (MI) every year [15, 16]. In the US, approximately 1.5 million individuals experience MI each year, and amongst them, majority are either hospitalized for unstable angina or for treatment of stable chest pain syndromes. Every year, nearly 735,000 adults in the US have a heart attack, among which 525,000 are a first heart attack and 210,000 are recurrent heart attacks [12]. Observational studies on patients recovering from an acute MI reported that 1 in 5 patients had recurring angina within one year, even after intensive treatment [17].

1.2.3 Morbidity – Disability due to CAD

Globally, the overall burden of CAD (measured in terms of disability-adjusted life years (DALYs)) is projected to increase to 82 million DALYs in 2020 from about 47 million in 1990 [18]. CAD is the leading cause of DALYs in the US for both males and females (11.2% of the total) [19]. In the global burden of disease report, US was ranked 12 among 15 countries for age-standardized rates of DALYs for CAD relative to comparator countries (where 1 indicated best performance and 15 worst performance) [20].

1.2.4 Morbidity – Health-Related Quality of Life (HRQoL)

Another aspect of morbidity is the humanistic outcomes, specifically HRQoL. Individuals with CAD may experience poor HRQoL due to the symptom burden, complications resulting from CAD, such as MI, limited physical functioning capacity, and psychological stress [21]. It is reported that patients with MI have lower HRQoL compared to those with heart failure. Another study indicated that 25-30% of individuals with cardiovascular event experience a constant feeling of uneasiness concerning their health, resulting in lower HRQoL [22]. Such lower HRQoL can lead to higher risk of mortality. A study by Bosworth et al (1999) observed 2,800 patients with CAD over period of 3.5 years. This study indicated that lower HRQoL was related to an approximately threefold greater all-cause risk of mortality and a 3.6-fold greater risk of mortality due to CAD [23].

1.2.5 Healthcare Utilization

The high burden of CAD can lead to intensive healthcare utilization. In the US, in 2010, there were 11 million ambulatory care visits, 10.5 million physician office visits, 587,000 emergency department visits, and 764,000 outpatient department visits with a primary diagnosis of CAD [4]. Further, Merrill et al (2008) indicated that 74.8% of emergency department visits for CAD resulted in hospital admission [24]. Among the elderly Medicare beneficiaries (≥ 65 years), of the average of 2.1 million hospitalizations per year, 42.0% of the visits occurred among those with CAD followed by heart failure (28.9%), cardiac dysrhythmia (17.8%), and other diseases of the heart (11.3%) [25].

1.2.6 Direct and Indirect Healthcare Costs

The direct healthcare costs of caring for individuals with CAD are substantial; direct medical care costs of CAD in the US is projected at \$106.4 billion in 2030, a 198% change from 2010 [26]. Nearly, 50% of direct healthcare costs can be attributed to the hospitalizations [27]. Hospital or inpatient expenditures may be higher because of invasive procedures needed to manage CAD. According to the Healthcare Cost and Utilization Project (HCUP) statistics (2012), the mean hospital charges for a vascular/cardiac surgery or procedure was \$78,897, cardiac revascularization was \$149,480, and percutaneous interventions was \$70,027 [4].

The costs due to lost productivity, have been estimated to be \$81 billion [4, 27]. The indirect costs measured as lost productivity from morbidity and premature mortality can also be very high [4, 27, 28]. According to Heidenreich et al (2011), the indirect costs attributed to CAD is expected to increase to \$112.3 billion in 2030 from \$73.2 billion in 2010 [26].

In summary, CAD affects millions of adults in the US and contributes to substantial burden in terms of mortality, morbidity, poor humanistic outcomes, healthcare utilization, and costs of care.

1.3 Management of CAD

Long-term management of all forms of CAD follows the guidelines established for stable CAD [27]. According to clinical practitioners the management of CAD has two main goals: (i) *to reduce symptoms and ischemia*; (ii) *to prevent MI and death* [29]. There are many components to CAD management and they include physical activity, smoking cessation, blood pressure (BP) control, lipid control, diabetes, prescription of antiplatelet agents, beta-blockers, renin-angiotensin-aldosterone system blockers, nitrates, calcium antagonists, and ranolazine, and influenza vaccine [27].

Among all the risk reduction strategies, lowering BP and low-density lipoprotein cholesterol (LDL-C) levels are central to achieving the main goals of CAD management. A report from National Health and Nutrition Examination Survey (NHANES) indicated that nearly 44% decline in CAD mortality over time was attributable to changes in risk factors. Among all the risk factors, lower total cholesterol (24%) and lower systolic BP (20%) accounted for most of the decline in mortality compared to lower smoking prevalence (12%) and decrease in physical inactivity (5%) [4].

Reducing of LDL-C is associated with a reduced risk of recurring cardiovascular events in individuals with a diagnosis of CAD [30-34]. Clinical trials and prospective studies have shown that reducing blood pressure in patients with CAD can improve survival and prevent recurrent MI or stroke [35, 36]. Based on robust evidence, the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure suggest lowering BP to 140/90 mmHg or less for patients with CAD [35]. Similarly, the Third Report of the National Cholesterol Education program recommends lowering LDL-C to less than 100 mg/dL in patients with CAD [37].

1.3.1 The Importance of Statin Therapy

For attaining guideline recommended LDL-C, pharmacotherapy that lowers lipid levels has become the standard of care for individuals with CAD. Although many types of lipid-lowering drugs (statins, bile acid sequestrants, fibrates, niacin, and ezetimibe) are available [37], statins are commonly prescribed for many reasons. The efficacy of statins in the primary and secondary prevention of cardiovascular events has been demonstrated by clinical trials [30-33]. For example, in the Cholesterol and Recurrent Events trial, pravastatin has been shown to reduce the risk of mortality, major coronary events, and the need for major invasive procedures compared to placebo [33].

In addition, statin therapy can be highly effective among older patients with CAD. Studies that have examined the effectiveness of statin therapy in reducing cardiovascular events and mortality in older patients suggest that older adults have greater reduction in coronary events as compared to younger subjects [38-40]. For example, among users of simvastatin, major coronary event rates were reduced by 32% in those ≥ 65 years of age versus 19% in those <65 years of age [39]. The differential was even more striking in terms of mortality, which decreased by 45%

in those ≥ 65 years of age compared to 11% in patients < 65 years of age [39]. Similar benefits among the elderly have been observed among Pravastatin users [38]. Statin therapy in the elderly has been projected to be cost-effective, where the incremental cost for quality-adjusted life year (QALY) in the elderly was reported to be \$18,800 much lower than the target of \$50,000 per QALY [41].

1.3.2 Antihypertensive Therapy

To attain guideline-recommended BP goals, antihypertensive pharmacological therapy is often prescribed for individuals with CAD. There are several antihypertensive drug classes such as beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), calcium channel blockers, diuretics, and others [35], each with their own mechanism of lowering BP. In addition, the efficacy and effectiveness of beta-blockers [42, 43] and ACEIs/ARBs [44-48] in reducing cardiovascular events among individuals with CAD have been proven.

1.3.2.1 The Importance of Beta-blockers, ACEIs, and ARBs

However, there is no convincing evidence on the superiority of the cardio-protective effect of one single antihypertensive drug class over the others. The choice of antihypertensive drug class is usually guided by the compelling indication [49, 50]. Beta-blockers are usually the first-line antihypertensive medication for individuals with CAD and are recommended for CAD patients [51]. Beta-blockers have also shown to be cost-effective in elderly patients [52]. As it has been established that ACEIs reduce the risk of death, MI, diabetes, and renal problems, ACEIs are recommended for individuals with CAD, specifically for those with diabetes to lower the risk of heart attack or heart failure. ARBs are prescribed to patients who cannot tolerate ACEIs [36]. ACEIs have demonstrated cost-effectiveness in the elderly Australian population; the incremental cost for QALY was reported to be 29,535 Australian dollars, which is much lower than the target of \$50,000 per QALY [53].

Because of the broad benefits of these agents, the American College of Cardiology Foundation and the American Heart Association recommend that statins and antihypertensive medications be initiated and maintained for the secondary prevention of CAD [27].

In summary, pharmacotherapy with statins and ACEIs/ARBs/beta-blockers is the mainstay of the effective CAD management.

1.4 CAD Management and the Role of Incident Cancer

It has been well documented that those with CAD have other co-existing conditions or at risk for developing new chronic conditions [54] and these conditions may compromise survival. Adults with CAD are more likely to develop other chronic conditions such as cancer, stroke, and congestive heart failure. Using the Duke Databank for Cardiovascular Diseases, Sachdev et al (2004) reported that co-existing chronic conditions were very common and

were associated with poor survival among individuals with CAD who had undergone medical treatment for CAD and followed for an average of 13.6 years [55].

Of these, the subsequent presence of incident cancer among individuals with CAD is especially important for many reasons: (i) CAD and cancer have shared risk factors and unique pathophysiology; (ii) adults with CAD are more likely to develop cancer; (iii) there can be negative effects of some cancer treatments on cardiovascular health; (iv) as both CAD and cancer are life-threatening conditions, the co-management of these conditions is especially challenging; and (v) both conditions are very costly to treat and manage and such heavy financial burden has implications for payers, healthcare providers and patients.

1.4.1 Shared Risk Factors

There is evidence that cardiovascular diseases including CAD and cancer share many biological (example: inflammation, oxidative stress, hyperglycemia, hypertension, hypertriglyceridemia) and behavioral risk factors such as obesity, tobacco use, and poor diet. Although the pathways between CAD and cancer are multifaceted and complex, these shared risk factors may lead to the development of cancer in individuals with CAD and vice versa [56]. For example, inflammation has been shown to mediate all stages (from initiation to progression, and thrombosis) of atherosclerosis, a precursor to CAD. Similarly, the role of inflammation in promoting carcinogenesis and tumor progression is well established, where inflammation promotes malignant transformation of cells, carcinogenesis, and its progression [56].

1.4.2 CAD as a Risk Factor for Cancer

Some studies have provided evidence of CAD as a risk factor for development of cancer. The findings from the REDUCE study demonstrated that CAD was associated with a 35% increased risk of developing prostate cancer [57]. An elevated risk of prostate cancer (adjusted odds ratio, 2.00; 95% confidence interval, 1.18-3.39) has been reported among adults with CAD [58]. Diagnosis of CAD has also been associated with increased risk of colorectal cancer; Chan et al (2007) reported significantly ($P<0.001$) higher prevalence of colorectal cancer in those with CAD (34.0%) compared to their counterparts (18.8%) [59].

1.4.3 Negative Effects of Some Cancer Treatments on Cardiovascular Health

While the goal of CAD management is to reduce coronary events, cancer treatments such as radiotherapy, chemotherapy, and hormone therapy can accelerate or worsen pre-existing cardiac disease [60-62]. Breast cancer treatments include chemotherapy (e.g., anthracyclines), surgery, radiation therapy, hormone therapy (e.g., tamoxifen), and targeted therapies (e.g., trastuzumab). Radiation therapy is of particular concern because of proximity to the heart, which can increase the risk of CAD or worsen pre-existing CAD resulting in major coronary events (e.g., heart attack) and even death. Anthracyclines and trastuzumab typically result in clinical heart failure or heart attack [63-65]. Androgen deprivation therapy (ADT) is the key therapeutic approach for metastatic prostate cancer and is also used in patients with a manifestation of disseminated disease with rising or elevated serum prostate-specific antigen. However, use of ADT increases the risk of CAD, the risk being further higher in those

with pre-existing CAD [66]. Colorectal cancer treatment comprises of surgery, chemotherapy (e.g., capecitabine, 5-fluorouracil, bevacizumab, etc.), and radiation therapy. The cardiotoxicity is mainly attributed to chemotherapeutic agents used for treating advanced and/or metastatic colorectal cancer. For example, patients receiving 5-fluorouracil have 45% risk of angina and 22% risk of MI. Capecitabine is metabolized to 5-fluorouracil, thereby results in cardiotoxicity [67].

1.4.4 Dominant Condition as the Driver of Treatments: CAD or Cancer?

Management of CAD in cancer patients is very challenging. Despite advancements in treatments, both CAD and cancer continue to be the leading causes of death [68]. Therefore, in medical decision making, in which life-threatening conditions are prioritized, cancer can be considered as dominant condition that “eclipses” the management of CAD [69], specifically among the elderly.

CAD-related care after cancer diagnosis may be prioritized because those with CAD may be at a higher risk for mortality compared to those without cancer. For example, it has been reported that women with breast cancer were at higher risk of mortality due to cardiovascular diseases as compared to women without breast cancer [70]. Furthermore, to reduce the negative effects of cancer treatment on cardiovascular health, providers may pay increased attention to CAD management, specifically the prescription of statins and ACEIs/ARBs/beta-blockers. A meta-analysis of randomized clinical trials and observational studies in general population indicated that statins, beta-blockers, and ACEIs/ARBs can reduce cancer treatment-related cardiotoxicity. Cardiac events were significantly reduced with beta-blockers (RR = 0.31 [95% CI 0.16–0.63], $P = 0.001$), statins (RR = 0.31 [95% CI 0.13–0.77], $P = 0.01$) and ACEIs/ARBs (RR = 0.11 [95% CI 0.04–0.29], $P < 0.0001$) [71]. In addition, it is recommended that patients with unstable angina or acute MI should be evaluated and stabilized before they undergo cancer-related surgery [72] suggesting that CAD management will be prioritized before cancer treatment.

On the other hand, cancer treatment may be prioritized because of “life-threatening” nature of the disease. Indeed, a patient with pre-existing CAD and incident cancer can be considered as a prototype example of a complex patient, as defined by Agency for Healthcare Research and Quality “two or more chronic conditions in which each condition might influence the care of the other condition, either through a limitation on life expectancy imposed by one of the conditions or because these two conditions generally entail therapies which are likely to have interactions with each other, or thirdly wherein one of these conditions might be requiring therapies that are contraindicated by the presence of the other conditions” [73].

1.4.5 Healthcare Expenditures: CAD and Cancer

Both CAD and cancer are very costly to treat and manage and such heavy financial burden has implications for payers, healthcare providers and patients. It has already been established that heart disease is a very expensive medical condition [74]. Individuals with cancer also have higher expenditures as compared to those without cancer [74]. In terms of average per-capita healthcare expenditures, heart disease and cancer were the first and second most expensive conditions in the US [75]. Among all heart diseases, CAD is the most expensive condition [26]. CAD-related expenditures are projected to increase from \$135.7 billion in 2010 to \$161.4 billion in 2020 [26]. Direct costs

of cancer are also projected to increase from \$124 billion in 2010 to \$158 billion in 2020 [76]. Diagnosis of incident cancer in individuals with pre-existing CAD can further result in increased costs resulting from cancer treatment-related cardiotoxicity.

In summary, incident cancer may play a crucial role in the management and CAD-related outcomes and costs, therefore, studies are needed to elucidate the relationship between incident cancer and pharmacotherapy for CAD management, CAD-related outcomes and healthcare expenditures.

1.5 Significance of the Study

To date, few studies have examined the management of CAD in elderly patients with pre-existing CAD and incident cancer. Such studies are warranted because of: (i) the relatively high burden of CAD as compared to other heart diseases; (ii) substantial disease burden of CAD among the elderly; (iii) high prevalence of CAD and cancer among the elderly; (iv) benefits of CAD-related pharmacotherapy for both CAD and cancer survival; and (v) cost implications of CAD and cancer.

1.5.1 Burden of CAD in Comparison to Other Heart Diseases

Among all the cardiac conditions, CAD is the most common form of heart disease in the US adults (≥ 18 years). In 2015, prevalence of CAD was 8.3% compared to other cardiac conditions, i.e., heart failure (3.0%) and stroke (3.4%) [26]. Based on National Center for Health Statistics (2008), CAD accounted for 49.9% of all cardiovascular deaths compared to stroke (16.5%), other cardiovascular disease (15.6%), hypertensive diseases (7.5%), heart failure (7.0%), and diseases of arteries (3.4%) [77]. Further, CAD accounted for \$46.8 billion in direct costs compared to heart failure (\$32.4 billion) and stroke (\$38.0 billion) [26].

1.5.2 Burden of CAD in the Elderly Population

The prevalence of CAD is highest among individuals 65 years and older; 19.8% of this population having CAD *versus* younger 8.4% among those under age 65 years [6]. Among 60 to 79 years' age group, approximately 25% of men and 16% of women have CAD, and the prevalence further rises in those 80 years and older, i.e., 37% and 23% among men and women, respectively [27]. In addition, about 80% of CAD-related mortality is reported in among elderly population (65 years and older) [4].

The rates of mortality and morbidity further increase with increase in age. CAD accounts for one-third to one-half of all deaths in the elderly Americans and about one in every four elderly CAD-related functional disabilities. In those above 65 years of age, about 8% die annually following MI and at least one half experience fatality related to other coronary events within 10 years. This mortality rate is double than that of individuals younger than 65 years of age [78]. In approximately 50% of patients, angina is the initial manifestation of CAD and the incidence of angina rises with increase in age [4]. Two population-based studies on elderly population (65 years and older) reported similar annual rates of MI in patients with symptoms of angina, i.e., 3% and 3.5% per year [79, 80].

Given the higher prevalence of CAD in the elderly population, nearly three-quarters of total expenditures for CAD can be attributed to the individuals aged 65 years and older [81]. Moreover, with the increase in the older adult population in the US, it has been projected that, relative to year 2010 (\$35.7 billion), expenditures for the treatment of CAD will increase 66% by the year 2030 (\$106.4 billion) [26], and the fastest growth rate in costs will be among the elderly population (≥ 65 years) [26].

CAD is the second leading cause of disability among older adults, and this attributes to lower self-reported HRQoL in this population. Cardiovascular complication resulting from unstable CAD negatively affect physical functioning and their ability to perform routine activities of daily living [82]. Although not specific to CAD, an association between cardiovascular disease and frailty, resulting in increased risk of disability [83] has been reported. Results from the cardiovascular health study indicated that the presence of cardiovascular disease in elderly participants was associated with a loss of approximately 5.6 years and 6.5 years of “successful” life (i.e. with good health and function) in men and women, respectively [84].

1.5.3 CAD and Cancer in the Elderly Population

Age is the most powerful non-modifiable risk factor for both CAD and cancer; the incidence of both cancer and cardiovascular disease increases with age [85-87]. Prevalence estimates indicate that 77% of all cancers are diagnosed in those aged 55 years or older. Similarly, the risk of CAD increases after the age of 55 years among men and 65 years among women [88, 89]. Amongst older individuals diagnosed with cancer, heart disease is the most common pre-existing condition; about 20% of elderly individuals with newly diagnosed cancer have some form of pre-existing cardiovascular condition [90]. Further, both CAD and cancer are the leading cause of morbidity and mortality in elderly population.

Investigators from the CORONOR study reported that individuals with CAD have similar mortality rates as those of the general population [91] and among surgically treated individuals with CAD, the 10-year survival rate was estimated at 77% [92]. Therefore, many individuals with CAD can survive to old age. As many types of cancers are often considered as the disease of the elderly, an individual may develop cancer after CAD.

1.5.4 Statins, Beta-blockers, ACEIs, and ARBs and CAD-related Outcomes

While beneficial effects of pharmacotherapy with statins and ACEIs/ARBs/beta-blockers for secondary prevention are proven for individuals with CAD, these benefits can be achieved and sustained only when individuals adhere to these medications over a period of time. Medication adherence, the “extent to which an individual takes medications as prescribed by their healthcare providers” [93], is associated with reduced risk of hospitalizations, recurrent coronary events, and cardiovascular mortality [94, 95]. Furthermore, adherence to both statins and antihypertensive therapies have been reported to reduce the relative risk of CAD mortality by 80% [96]. In addition, optimal adherence to these pharmacotherapies significantly reduces annual costs for secondary prevention of CAD; between \$294 and \$868 per patient, accounting to 10.1% - 17.8% cost reductions between adherent and non-adherent groups [94].

1.5.5 Cost Implications of CAD and Cancer in the Elderly Population

An overwhelming percent (96%) of the expenditures among the elderly are due to multiple chronic conditions [97, 98]. Cancer and heart disease are two of the most expensive conditions [75]. As 84% of the elderly over 65 years of age are covered by Medicare [99], this has implications for healthcare financing reforms. As policy makers and providers have priorities better health, better value and lower costs, it is important to understand the financial burden of CAD and cancer for program, policy planning, and allocation of resources.

To summarize, incident cancer plays a crucial role on CAD-related pharmacotherapy, outcomes, and expenditures.

1.6 Need for the Study

However, there is paucity of research on the impact of cancer on CAD-related pharmacotherapy, outcomes, and expenditures. There is a need for studies that exclusively focus on CAD-related pharmacotherapy, outcomes and expenditures among elderly fee-for-service (FFS) Medicare beneficiaries with incident breast, colorectal and prostate cancer because: (i) Medicare covers 84% of the elderly population and the primary payer of healthcare for the elderly; (ii) elderly share a disproportionate burden of CAD; and (iii) the cancer of breast, prostate, and colon/rectum, and lung/bronchus are the most common invasive cancers in the US.

1.6.1 Medicare as the Primary Payer of CAD and/or Cancer

Nearly 84% of the elderly are covered by Medicare. Payments made by Medicare for CAD are substantial. For example, in 2003, the Medicare program paid \$12.2 billion for CAD-related hospitalizations, including \$12,321 per discharge for acute MI and \$11,783 per discharge for coronary atherosclerosis [100]. Similarly, Medicare payments for treatment of cancer totaled \$29 billion in 2006. In addition, \$2 billion were spent on drugs to treat the side-effects of chemotherapy [101].

1.6.2 Disproportionate Burden of CAD among Elderly Population

As discussed earlier, elderly population share a disproportionate burden of CAD [4]. Similarly, burden associated with cancer is also higher among elderly population [102]. Further, the prevalence of CAD is higher among elderly Medicare FFS beneficiaries, with 34% of beneficiaries aged 65 years and older were diagnosed with CAD compared to 19% of younger beneficiaries (aged <65 years) [97, 103]. Similarly, prevalence of cancer is higher among elderly Medicare beneficiaries [101]. As Medicare is the primary payer for healthcare expenditures for elderly Medicare beneficiaries [104], with nearly 42.9 million enrolled (based on 2013 enrollment in Medicare Part A and/or B) [99], it is important to focus on this population.

1.6.3 CAD and Common Cancers

The cancer of breast, prostate, colon/rectum, and lung/bronchus are the most common invasive cancers in the US population. Based on the Centers for Disease Control and Prevention statistics (2011), breast, lung, and colorectal cancer have the highest incidence rates among all female cancer cases; rates per 100,000 women are

122.0, 52.0, and 34.9, respectively. Prostate, lung, and colorectal cancer have the highest incidence rates among all male cancer cases; rates per 100,000 men are 128.3, 73.0, and 46.1, respectively [105]. Three cancer sites – breast, prostate, and colorectal cancers have been selected because of the availability of commonly used screening modalities and the existence of competing therapies. Further, with the currently available screening tests, these three cancers have a higher probability of diagnosis at an earlier stage compared to lung cancer, and thus improved survival rates. The estimated 5-year relative survival rate is 91% for women with breast cancer, 66% for patients with colorectal cancer, and 99% for patients diagnosed with prostate cancer, whereas it is only 18% for lung cancer [106]. These cancers are common among older adults (≥ 65 years). Based on the Surveillance, Epidemiology, and End Results (SEER) Program 2008-2012 statistics, incidence of breast cancer (41.8%), colorectal cancer (58.6%), and prostate cancer is 41.8%, 48.6%, and 56.7%, respectively [107]. In addition, prevalence of MI and CAD in elderly population with breast, colorectal or prostate cancer is about 15.4%, 7.4% or 6.1% and 10.2%, 16.0% or 16.5%, respectively [108-114]. Thus, CAD and incident cancer are highly prevalent in common cancers such as breast, colorectal and prostate cancers.

To summarize, studies on evaluating the relationship between incident cancer and CAD-related pharmacotherapy adherence, and expenditures and the broad benefits of CAD-related pharmacotherapy adherence on CAD-related outcomes among elderly cancer patients are needed for informing clinical practice, research, program planning, and allocation of resources. However, there are critical gaps in knowledge because of paucity of studies in this area. The present dissertation is aimed at addressing these aforementioned critical gaps in knowledge by focusing on a cohort of elderly Medicare beneficiaries with pre-existing CAD and a diagnosis of incident breast, colorectal or prostate cancer.

1.7 Specific Aims

The specific aims, objectives, and hypothesis of the dissertation are as follows.

Aim 1: Examine the relationship between incident cancer and adherence to statins and/or ACEIs/ARBs/beta-blockers among elderly fee-for-service Medicare beneficiaries with pre-existing CAD by comparing those with incident (breast, colorectal, and prostate) cancer and without cancer.

Hypothesis: Adherence to CAD-related concomitant pharmacotherapy will be lower among elderly Medicare FFS beneficiaries with CAD and incident cancer as compared to those with CAD and no cancer.

Aim 2: Examine relationship between adherence to both statins and ACEIs/ARBs/beta-blockers and CAD-related hospitalizations among elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, or prostate cancer, after controlling for cardiotoxic cancer treatments and other risk factors that may affect CAD-related hospitalizations.

Hypothesis: Better adherence to concomitant therapy will be associated with lower risk of CAD-related hospitalizations, after controlling for cancer treatment and other risk factors.

Aim 3: Estimate the association between incident cancer and short-term CAD-related healthcare expenditures by comparing the elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident cancer to their counterparts with CAD and no cancer.

Hypothesis: The short-term CAD expenditures will be higher among those with CAD and incident cancer as compared to those with CAD and no cancer.

1.8 Innovation and Unique Contribution of the Study

Cardio-oncology or onco-cardiology is an emerging field and most of the existing evidence on management of heart diseases in individuals with cancer is based on clinical expert opinion. There is paucity of studies on the influence of cancer diagnosis on management of CAD. Our study will contribute to the nascent literature on management of CAD in patients with cancer. There are several facets of our study that makes it unique and important for understanding the impact of cancer on CAD related medication adherence, outcomes, and healthcare expenditures.

First, the current dissertation fills a critical knowledge gap on the management of chronic conditions among cancer survivors has been very limited. It is important to recognize ways in which pre-existing conditions could affect the health of cancer patients so that patient-centered care and individualized treatment can be achieved [115].

Second, our study can illuminate the complex relationship between CAD management and incident cancer. Prior studies have suggested that cardiovascular disease management is compromised in cancer patients. A study utilizing Medicare-linked database examined management of cardiovascular disease in older women (≥ 65 years) with breast cancer and concluded that these women received inadequate treatment and care for heart problems. Their study findings indicate that about 12% of these older women with breast cancer developed heart failure within three years of cancer diagnosis and treatment. Further, the findings indicate that only 33% of these patients saw a cardiologist within 90 days of developing heart problems [116]. Another study, examined quality of care for chronic disease, such as cardiovascular disease, diabetes, and hypertension in cancer survivors, and concluded that the cancer survivors received inadequate care for these chronic conditions compared to those without cancer [117].

Third, this study is a population-based study utilizing “real-world” data. It has been pointed out by the investigators of the CLARIFY study among individuals with stable CAD that real-world studies on CAD are needed because “clinical trials or registries which often have stringent exclusion criteria, and do not adequately represent populations with stable CAD (in terms of age, comorbidity, and concomitant therapy)” [118]. The current dissertation highlights the importance of real-world studies.

Fourth, this dissertation focuses on elderly population and it is estimated that by 2050, there will be 83.7 million over the age of 65 [119]. Both CAD and cancer are highly prevalent in aging population. Further, it has been previously reported that elderly patients are under-represented in clinical trials, with individuals older than age 65 years representing only 38% of enrolled patients, specifically those with comorbid conditions [120]. Understanding the influence of life events such as cancer diagnosis on management of pre-existing chronic conditions are important to the growing elderly population with multiple chronic conditions. Our proposed study is the next best alternative to clinical trials for understanding this relationship.

Fifth, this dissertation focuses on elderly FFS Medicare beneficiaries. As discussed earlier, Medicare is the primary payer of healthcare for elderly in the US [104]. Therefore, Medicare bears the largest share of the clinical, humanistic, and economic burden in this population. The findings from this study will have implications for the various healthcare delivery and financing reforms such as the establishment of accountable care organizations, patient-centered medical home and others undertaken by the Centers for Medicare and Medicaid Services, which is responsible for setting policy priorities and healthcare payments.

Sixth, this dissertation can provide insight into co-management for multiple conditions. CAD and cancer share a unique relation. In general, it is difficult to manage multiple health conditions in elderly patients as treatment of one medical condition may interfere with treatment of other medical condition [73]. There is paucity of evidence on CAD management in patients with cancer. The study findings may be useful in understanding the influence of cancer on CAD management.

1.9 Conceptual Framework

The selection of variables was guided by conceptual frameworks and these differed by specific aims.

1.9.1 Conceptual Framework: Aim 1

A conceptual framework by Park and Jones was adapted for understanding influence of cancer on adherence to cardiovascular medications among elderly population. This model considers patient-related factors, health-system factors, provider factors, and external environment. This model has also been used previously by Gellad et al (2009) for understanding factors that affect adherence to medications in elderly population [121]. The conceptual framework is shown in Error! Reference source not found..

Figure 1.1 Conceptual framework adapted from Park and Jones for medication adherence.

Abbreviations – CAD: Coronary artery disease; SEER: Surveillance, Epidemiology, and End Results

1.9.2 Conceptual Framework: Aim 2 and Aim 3

The Andersen behavioral model of health service use and outcomes was adapted for this study as it provides an appropriate framework for understanding the relationship between explanatory variables and outcomes. This framework also provides basis for selecting other independent variables that may influence CAD outcomes [122, 123].

This original model was developed by Andersen and his colleagues in 1968 and has been used to examine various types of healthcare utilization in elderly population with chronic conditions. It is a multi-level model that includes both individual and contextual determinants of healthcare utilization and categorizes these determinants into predisposing, enabling, and need factors, personal health practices/ health behavior, and external environment [124, 125].

The predisposing factors are the individual's demographic characteristics which decide their proclivity towards healthcare utilization. Factors such as age, sex, and race/ethnicity are "biological imperatives" that influence their unique predisposition towards use of healthcare services. The enabling factors include resources available to each individual that enable them to obtain services. In the context of this study, these factors include marital status, Medicaid coverage (insured, uninsured), education, income, and poverty status. The need-based factors at the individual level are those related to the perceived need for health services due to functional and health problems. In the context of this study, need-based variables include cancer type, stage of cancer, cancer treatment, comorbid chronic physical conditions, and mental health conditions. The personal health practices include tobacco use, alcohol abuse, and healthcare-seeking behavior. The external environment includes following variables for this study - SEER region, area of residence, health professional shortage area (HPSA), county level number of oncologists and cardiologists, and centers for cardiovascular care. The conceptual framework for CAD-related hospitalizations as the outcome is shown in **Figure 1.2** and for CAD-related healthcare expenditures as the outcome is shown in **Figure 1.3**

Figure 1.2 Conceptual framework adapted from the Andersen Behavioral Model of Health Service Use for medication adherence and health outcomes.

Abbreviations – CAD: Coronary artery disease; PCP: Primary care physician; SEER: Surveillance, Epidemiology, and End Results; SES: Socioeconomic status

Figure 1.3 Conceptual framework adapted from the Andersen Behavioral Model of Health Service Use for medication adherence and economic outcome.

Abbreviations – CAD: Coronary artery disease; PCP: Primary care physician; SEER: Surveillance, Epidemiology, and End Results; SES: Socioeconomic status

1.10 Data Sources for the Study

Data for the study population will be derived from the SEER-Medicare linked files. The comparison group of non-cancer patients will be derived from the non-cancer 5% sample files. The files will also be linked to the Area Health Resources File (AHRF), census tract files, and county health ranking files.

1.10.1 SEER-Cancer Registry

SEER program is an epidemiologic surveillance system consisting of population-based tumor registries that collect data on all incident cases of cancer that occur in persons residing in 18 SEER areas. These areas include Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles and San Jose-Monterey, Rural Georgia, Alaska Native, Greater California, Kentucky, Louisiana, New Jersey, and Greater Georgia. SEER data also consists of information about demographic characteristics of the patient, diagnosis date, cancer site, stage, and grade, and type of surgical treatment and radiation therapy provided within 4 months of diagnosis [126]. The Patient Entitlement and Diagnosis Summary File (PEDSF) contains all of this information from the SEER program.

1.10.2 Medicare

Medicare is the primary health insurance provider of US population above 65 years of age and thus, SEER data have been linked to Medicare claims. This database consists of the following files - Medicare Provider Analysis and Review (MEDPAR), the Carrier Claims (old name National Claims History (NCH) from physician/supplier), Outpatient, Home Health Agencies (HHA), Hospice, Durable Medical Equipment (DME), and Part D Event (PDE) files. The MEDPAR file includes hospital claims for all short- and long-term and skilled nursing facility stay. The NCH file contains claims from physicians and other non-institutional care providers and has procedure codes according to the *Health Care Procedure Classification Code (HCPCS)* and the *Common Procedural Terminology, 4th Edition (CPT-4)*, and the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* procedure codes with service dates. The outpatient file includes claims from institutional outpatient providers, including hospitals, rural health clinics, and mental health centers.

Part A of the Medicare program consists of the following types of services - inpatient hospitalization, Skilled Nursing Facility (SNF), home health agency services (HHA) following hospital stay and hospice care. *Part B* of the Medicare program includes physician services, outpatient services, diagnostic test, DME, emergency room visits, home health care not following a hospital stay, laboratory services, and other medical services. *Part D* of the Medicare program covers prescription drugs. The Medicare started providing voluntary outpatient medications coverage (Part D) since January 2006, and hence Part D data is available only after 2006.

1.10.3 SEER-Medicare

The Medicare data files have been linked with PEDSF file of cancer cases from SEER using an algorithm based on the social security number, last name, first name and date of birth of an individual. Approximately 94% of the SEER cancer cases over age 65 years with Medicare enrollment have been linked using this method [126]. Based on

the linkage, a common encrypted identification number is given to each enrollee in PEDSF and claims files. Each record represents an episode of hospital stay. These records can have up to 10 diagnoses (ICD-9-CM codes) for each date of admission and date of discharge.

1.10.4 SEER Non-Cancer Medicare

SEER non-cancer Medicare database also provides a 5% non-cancer random sample from Medicare program in the same catchment areas as those in SEER program that can be used to compare cancer and non-cancer case. The Summarized Denominator file (SUMDENOM) provides demographic information. These beneficiaries are randomly selected based on the last two digits of their social security number [126]. The individuals who have been reported to SEER with an incident cancer are removed from this 5% random sample. The demographic and other Medicare enrollment data for non-cancer cases are identical to those of cancer cases and can be linked with the cancer files using each beneficiary's unique Medicare claim number [127].

1.10.5 American Community Survey (ACS) Census Tract Files

The ACS 2008 to 2012 census tract and census zip code files were linked to PEDSF files by geographic codes, i.e., state and county [128]. These files provided information on the census tract median household income and education level.

1.10.6 AHRF File

The AHRF is a publicly available data file provided by Department of Health and Human Services and contains county, state and national files. The AHRF provides more than 6,000 variables for each of the nation's counties. The AHRF contains information such as health facilities, health professions, and socioeconomic and environmental characteristics. The basic file contains geographic codes and descriptors that can be used to link it to other files and to aggregate counties into various geographic groupings [129]. This study will use the AHRF variables to measure health care infrastructure and socio-economic status of the counties that can influence medication adherence, CAD-related outcomes and healthcare expenditures.

1.10.7 County Health Ranking File

The county health ranking file was linked to PEDSF files by geographic codes, i.e., state and county. These files provide a snapshot of a community's health, such as rates of smoking, obesity, and other health status measures at the county-level [130]. These variables can be used as a proxy for external health environment that can influence medication adherence, CAD-related outcomes and healthcare expenditures.

CHAPTER 2

Incident Cancer and Adherence to Statins and Antihypertensive Medications for Coronary Artery Disease among Elderly Medicare Beneficiaries

2.1 Abstract

Objectives: To examine the relationship between incident cancer and adherence to statins and angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or beta-blockers among elderly individuals with coronary artery disease (CAD).

Methods: This was a retrospective observational longitudinal study assessing elderly Medicare fee-for-service beneficiaries with pre-existing CAD and those with incident breast (BC), colorectal (CC), or prostate (PC) cancer ($N = 12,096$) and those with no cancer (NC) ($N = 42,805$). Adherence to pharmacotherapy was measured every 120 days during the one-year pre- and one-year post-index period. Due to the overlap between cancer type and sex, cancer diagnosis was grouped into: (1) women with BC; (2) women with CC; (3) women with NC; (4) men with PC; (5) men with CC; and (6) men with NC. Medication adherence was categorized into five mutually exclusive groups: (1) adherent to both statins and ACEIs/ARBs/beta-blockers; (2) not adherent to both statins and ACEIs/ARBs/beta-blockers (reference group); (3) adherent to either statins or ACEIs/ARBs/beta-blockers; (4) use of one medication class and adherent to that class; and (5) use of one medication class and not adherent to that medication class. The adjusted relationship between incident cancer and medication adherence was analyzed using the generalized estimating equation. Inverse probability treatment weights were used to account for observed group differences between cancer and non-cancer groups.

Results: Only 28.9% of the elderly with CAD were adherent to both statins and ACEIs/ARBs/beta-blockers. In the adjusted analyses, women [AOR = 0.70; 95% CI = 0.58, 0.81; $P < 0.0001$] and men [AOR = 0.63; 95% CI = 0.51, 0.75; $P < 0.0001$] with CC and men with PC [AOR = 0.92; 95% CI = 0.85, 0.99; $P = 0.022$] were significantly less likely to be adherent to both medication classes compared to women and men with NC, respectively. No significant differences in adherence to medications were observed among women with BC compared to women with NC. Even among those using single medication class, women [AOR = 0.64; 95% CI = 0.50, 0.79; $P < 0.0001$] and men with CC [AOR = 0.59; 95% CI = 0.42, 0.76; $P < 0.0001$] were significantly less likely to be adherent to that medication class compared to women and men with NC.

Conclusions: Adherence to evidence-based medications for CAD varied by cancer types. Elderly Medicare beneficiaries with CC or PC were less likely to be adherent to evidence-based medications for CAD. Future research needs to explore the effect of non-adherence to concomitant medications on health outcomes such as survival among patients with incident CC and PC.

2.2 Introduction

The two main goals of coronary artery disease (CAD) management are reduction of symptoms and ischemia as well as prevention of myocardial infarction and death [29]. The use of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, and statins has become the standard of treatment among individuals with CAD. These medication classes have proven to reduce the risk of major coronary events [27], hospitalizations for CAD and recurrent coronary events [94, 95], and cardiovascular mortality by 11–35% [131, 132] through improving lipid and blood pressure control [94, 133]. Therefore, CAD management guidelines recommend initiating and maintaining these regimens indefinitely in adults with CAD [27, 134].

Further, adherence to combined use of statins and ACEIs/ARBs/beta-blockers have been reported to reduce the relative risk of CAD mortality by 80% [96]. On the contrary, non-adherence to statins has been shown to increase the risk of adverse cardiovascular events (myocardial infarction, heart failure, or stroke) and mortality [94]. Nevertheless, non-adherence to statins, beta-blockers, and ACEIs/ARBs is common in the elderly with cardiovascular disease [135–138]. A study on elderly Medicare beneficiaries discharged from the hospital after their first myocardial infarction reported that only 46.4% were adherent to beta-blockers, ACEIs/ARBs, and statins [138].

While many patient, provider, and health-system factors affect medication adherence in the elderly [139–142], development of an additional chronic condition may also impact adherence. Since both CAD and cancer are life-threatening conditions, it may be challenging to effectively manage both simultaneously. Some types of cancer can be considered as a dominant condition that “eclipse” the management of CAD [69], whereas other types of cancer with a higher expected cure rate, CAD-related care after cancer diagnosis may be particularly important in order to reduce the probability of CAD morbidity and mortality due to cancer-related treatments like surgery [72], chemotherapy, and radiation [60, 61]. Some medications designed for CAD may even have anti-cancer properties, as recent epidemiological studies suggest additional benefits of statins in terms of reduced cancer recurrence and cancer-specific mortality among individuals with breast [143], colorectal [144], and prostate cancer [145, 146].

However, there is paucity of studies examining adherence to CAD medications in the context of a new cancer diagnosis. Calip et al reported a decline in adherence to statins (average medication possession ration (MPR) = 0.78 vs. 0.68; $P < 0.001$) in the period just after breast cancer diagnosis [147], but the findings from this study may be limited because it did not include a non-cancer comparison group. Without a non-cancer comparison group, it is not known whether adherence decline is due to cancer or due to the passage of time. Furthermore, the findings may not be generalizable to other cardiovascular medications like ACEIs/ARBs/beta-blockers, or elderly patients. Data assessing medication adherence among the elderly is particularly limited [148], despite the fact that both cancer [102] and CAD [4] disproportionately affect the elderly. In the United States (US), the prevalence of CAD is higher among the elderly (19.8%) compared to those under age 65 years (8.4%) [6]. Nearly 80% of CAD-related mortality is reported among the elderly population [4]. Similarly, breast, colorectal, and prostate cancer are very common among the elderly, with 42.3%, 57.7%, and 56.9% suffering from these cancers, respectively [107]. Examination of adherence to statins and ACEIs/ARBs/beta-blockers among the elderly is also important for policy purposes because

Medicare provides coverage for almost all of the elderly in the US [99] and Medicare payments for CAD [100] and cancer care [101] are substantial.

Therefore, the primary objective of the current study is to examine the relationship between incident cancer and adherence to statins and/or ACEIs/ARBs/beta-blockers among elderly Medicare beneficiaries with pre-existing CAD by comparing those with incident (breast, colorectal, and prostate) cancer and without cancer.

2.3 Methods

2.3.1 Conceptual Framework

The conceptual framework by Park and Jones [121, 149] was adapted to select factors that can influence adherence to pharmacotherapy among elderly patients with CAD (**Figure 1.1**). This framework posits that patient-related factors (e.g., age, sex, race, census tract education level, poverty status, co-existing chronic physical and mental health conditions, tobacco and alcohol use), health-system (e.g., Medicare coverage gap), provider-related factors (e.g., visits to primary care and cardiologist), and environmental factors (e.g., Surveillance, Epidemiology and End Results [SEER] region, county metro status, community health clinics, county-level health professional shortage area [HPSA], and percent of cardiologists and oncologists in the county) affect medication adherence.

2.3.2 Study Design

The study utilized a retrospective observational longitudinal cohort design with 12-month pre- and 12-month post-index period (**Figure 2.1**). Pre- and post-index periods were defined based on cancer diagnosis dates for the cancer cohort. For the non-cancer cohort, pre- and post-index periods were derived using pseudo-diagnosis dates randomly selected from the dates of service. A 36-month window, divided into a 24-month baseline (for identification of CAD and baseline characteristics) and a 12-month (pre-index) periods were created. The post-index period consisted of 12 months after the index date. Adherence to statins and ACEIs/ARBs/beta-blockers and selected variables were measured repeatedly every 120 days during the pre- and post-index period, yielding a total of six repeated measures for each individual. Thus, t_1 , t_2 , and t_3 represented the pre-index period and t_4 , t_5 , and t_6 represented the post-index period.

Figure 2.1. Schematic presentation of study design

The longitudinal design with repeated measurement of adherence and other variables enabled tracking of the variability of adherence within and between individuals. By including a non-cancer comparison group, the study avoids the maturation threat to internal validity (i.e. the processes within subjects which act as a function of the passage of time).

2.3.3 Data Sources

Linked data from the following sources was utilized: 1) the SEER registries; 2) Medicare claims linked with the SEER registries; 3) 5% non-cancer random sample of Medicare beneficiaries in SEER region; 4) the American Community Survey (ACS), and 5) the Area Health Resource Files (AHRF). SEER program is an epidemiologic surveillance system consisting of population-based tumor registries that collects data on all incident cases of cancer that occur in persons residing in 18 SEER areas. SEER data also consists of information about demographic characteristics of the patient, diagnosis date, cancer site, stage, and grade, and type of surgical treatment and radiation therapy provided within four months of diagnosis [126]. Individuals without cancer were identified from the 5% non-cancer random sample of Medicare beneficiaries living in same catchment areas as those in SEER program. These beneficiaries were randomly selected based on the last two digits of their social security number [126]. We derived information on the census-tract level poverty status and education from the ACS [128]. The individuals who have been reported to SEER with an incident cancer are removed from this 5% random sample. County-level healthcare environment factors (community health clinics, HPSA, and percent of cardiologists and oncologists in the county) were derived from the AHRF [129].

2.3.4 Study Population

The study population comprised individuals with pre-existing CAD and those with incident breast, colorectal, or prostate cancer and those without cancer. Individuals with CAD were identified using a validated algorithm developed by the Centers for Medicare and Medicaid Services (CMS) [150] to identify individuals with pre-existing CAD. The algorithm used the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes. Individuals with at least one inpatient, outpatient and carrier claims (clinician encounters only), or home health agency service Medicare claims with a primary or secondary diagnosis of CAD during the baseline were classified as having pre-existing CAD.

Cancer and No Cancer Comparison Groups: Individuals with incident cancer, January 2008 through December 2011, were identified using the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) codes from the SEER registries. Individuals without cancer were identified from the 5% non-cancer Medicare claims from the SEER regions.

Other inclusion criteria were age 68 years or older, alive with continuous FFS Medicare Part A, B enrollment during the entire study period, continuous part D enrollment during the pre- and post-index period, no missing information on county, and who had two or more prescriptions for either statins or two prescriptions for any or combinations of ACEIs, ARBs, or beta-blockers. In the non-cancer cohort, individuals with end-stage renal disease were excluded prior to diagnosis date assignments. In the cancer cohort, individuals with missing data for type and

stage of cancer and those who were diagnosed with cancer through autopsy or death certificate were excluded. The selection criteria are presented in **Figure 2.2**.

2.3.5 Measures

2.3.5.1 Dependent Variable: Adherence to Statins, ACEIs/ARB/Beta-blockers

As this paper focuses on adherence over a long period of time, proportion of days covered (PDC) measure was used. PDC has been recommended by the Pharmacy Quality Alliance [151] and used by the CMS in its rating of insurance plans [152]. Statins, ACEIs, ARBs, and beta-blockers were identified using the generic names in the Part D Prescription Drug Event files. PDC of these medication classes were calculated only among those who filled at least two prescriptions for either statins or two prescriptions for ACEIs, ARBs, or beta-blockers. PDC was calculated as number of days of medication supplied during each time period (example: t_1) divided by the number of days in each time period (i.e. 120 days). For those with a drug regimen (i.e. statins and ACEIs/ARBs/beta-blockers), PDC considers days within a particular period when an individual is covered for both statins and ACEIs/ARBs/beta-blockers. PDC ranges from 0 to 1. Individuals with $PDC \geq 80\%$ were considered as adherent and those with $PDC < 80\%$ as non-adherent [153].

We combined the adherence indicator (yes/no) and the type of drug regimens and classified individuals with CAD into five mutually exclusive groups: (1) adherent to both statins and ACEIs/ARBs/beta-blockers; (2) not adherent to both statins and ACEIs/ARBs/beta-blockers; (3) adherent to either statins or ACEIs/ARBs/beta-blockers; (4) use of one medication class and adherent to that class; and (5) use of one medication class and not adherent to that medication class. This provides more granularity to the understanding of medication adherence based on use and adherence.

2.3.5.2 Key Independent Variable: Cancer Type and Sex

As the study included sex-specific cancers (breast and prostate cancer), the key independent variable was categorized into six mutually exclusive groups: women with breast cancer (BCW), women with colorectal cancer (CCW), women with no cancer (NCW), men with prostate cancer (PCM), men with colorectal cancer (CCM), and men with no cancer (NCM).

Figure 2.2. Schematic presentation of selection criteria for study cohort.

Abbreviations – ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; BB: Beta-blockers; CAD: Coronary artery disease; HMO: Health Maintenance Organization; R_x: Prescription

In the non-cancer cohort, individuals with end-stage renal disease were excluded prior to diagnosis date assignments.

2.3.5.3 Other Independent Variables

Patient-related factors

These were time-invariant except when specified otherwise and were measured during baseline. These included (i) demographics – age in years measured at index month of incident cancer diagnosis, sex, and race/ethnicity; (ii) census-tract socioeconomic status - poverty status and education level; and (iii) CAD severity – a proxy measure was used for CAD severity based on the CMS hierarchical condition category (HCC) classification system. Based on the CMS risk adjustment model, each of the HCC codes for CAD was assigned specific score based on the risk and severity [154], ranging from 0.231 to 0.349. Thus, higher scores represented severe manifestations of CAD.

Other physical and mental health conditions were selected based on the suggestions of the Multiple Chronic Conditions working group [155]. These were categorized into concordant (cardiac arrhythmias, congestive heart failure, diabetes, hyperlipidemia, hypertension, and stroke) and discordant (dementia, asthma, chronic obstructive pulmonary disease, arthritis, hepatitis, human immunodeficiency virus, and osteoporosis) conditions. Mental health conditions included severe mental illness (measured at baseline) and anxiety, depression, tobacco use, and alcohol use (measured every 120 days).

Health-system factors

Medicare Part D coverage gap was measured every 120 days. Part D plans typically start with an annual deductible, after which Medicare pays for the prescription drugs up to an initial coverage limit with certain coinsurance associated with those payments. The plan stops coverage once an individual reaches the annual coverage limit until the cost of prescription drugs reaches to catastrophic limit. The phase between the annual coverage limit and catastrophic coverage is called "donut hole" or "Medication coverage gap". During this period, enrollees have to bear the entire prescription drug costs. [156]. Based on their status of coverage, patients were categorized into three groups – not reached, reached, exceeded donut hole.

Provider-related factors

This included visit to primary care physician or cardiologist (yes/no), measured every 120 days.

Environmental factors

This domain included SEER region – Northeast (Connecticut, New Jersey), South (Kentucky, Louisiana, Atlanta, rural Georgia, and Greater Georgia), North-central (Detroit, Iowa), and West (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, Greater California), county metro status (metro and non-metro), based on urban/rural continuum codes from the AHRF, community health resources – (county-level community health clinics, county-level health professional shortage area (HPSA), and percent cardiologists and oncologists in the county). These were measured at baseline.

2.3.6 Statistical Analyses

Unadjusted subgroup differences in time-invariant characteristics between cancer and non-cancer cohorts were tested with chi-square statistics. As medication adherence was measured every 120-days during pre- and post-index period, each individual had six observations. These six observations were not independent and applying standard regression techniques can lead to misleading results. Therefore, the unadjusted and adjusted relationship between cancer and medication adherence were analyzed with a repeated measures design using the generalized linear mixed models (GLMM), which can accommodate both linear and non-linear outcome variables. Mixed-effects models are very useful in modeling both within and between subject variations. Some non-linear models that can be considered for repeated measures include population-averaged (PA) and subject-specific (SS) models [157]. For categorical outcomes, the generalized estimating equations (GEE) is often used to model PA effects and random-effects logistic regressions can be used to estimate SS effects. Under the GEE approach, the correlation between repeated measures within an individual is accounted by a robust estimation, even when the dependency is misspecified [158]. In this study, the PA approach was chosen because the objective is to estimate the average differences in adherence between cancer and non-cancer cohorts.

The adjusted GEE model controlled for time, age, race/ethnicity, census tract education level, poverty status, chronic physical and mental health conditions, tobacco use, alcohol use, Medicare coverage gap, visits to primary care and/or cardiologist, SEER region, county metro status, community health clinics, county-level HPSA, and percent of cardiologists and oncologists in the county.

2.3.6.1 Inverse Probability Treatment Weights (IPTW)

Our preliminary analyses indicated that there were significant group differences in sex, age, race/ethnicity, SEER region, and index year between the cancer and non-cancer cohorts. Therefore, we derived the IPTW and used these weights to adjust for these observed differences between cancer and non-cancer cohorts. We derived IPTW from the probability of cancer or no cancer based on a logistic regression on cancer and non-cancer with sex, age, race/ethnicity, SEER region, and index year as independent variables. The inverse probabilities of cancer or no cancer were used as weights in medication adherence analyses. Such weighting allows balancing of sex, age, race/ethnicity, SEER region, and index year between the cancer and non-cancer cohorts. **Table 2.1** summarizes the findings from the logistic regression model used to calculate IPTW.

2.4 Results

2.4.1 Characteristics of the Study Population Before and After IPTW Adjustment

The study population comprised 54,901 elderly FFS Medicare beneficiaries with pre-existing CAD (12,096 with cancer and 42,805 without cancer). **Table 2.2** summarizes the characteristics of cancer and non-cancer cohorts before and after IPTW adjustment. Prior to adjustment, those with cancer were less likely to be women than men (47.2% vs 62.5%), more likely to be younger than older (example: 80 or older) (66.3% vs 57.2%), and more likely to be Whites than African Americans, Hispanics, or other groups (82.1% vs 77.8%). After adjusting with IPTW, there were no significant differences in sex, age, race/ethnicity, SEER region, and index year between the cancer and non-cancer cohorts.

Table 2.1. Logistic Regression Models used to derive IPTW–Cancer and 5% Non-Cancer Sample

Characteristics	OR	95% CI	Significance
Age groups			
68-70 years	1.03	[0.97,1.10]	
71-74 years	1.33	[1.26,1.41]	***
75-79 years	1.36	[1.29,1.44]	***
80 years or older		<i>Reference</i>	
Sex			
Female	0.52	[0.50,0.55]	***
Male		<i>Reference</i>	
Race/Ethnicity			
African Americans	0.96	[0.89,1.04]	
Hispanics	0.61	[0.54,0.69]	***
Others	0.57	[0.52,0.62]	***
Whites		<i>Reference</i>	
SEER Region			
Northeast	1.13	[1.06,1.19]	***
South	0.98	[0.93,1.04]	
North-central	1.25	[1.17,1.34]	***
West		<i>Reference</i>	
Index year			
2008	1.07	[1.00,1.13]	*
2009	1.04	[0.98,1.10]	
2010	0.98	[0.93,1.04]	
2011		<i>Reference</i>	

Asterisks represent significant differences in study population characteristics (time-invariant), *non-cancer group* (reference category) for dependent variable.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

Abbreviations

IPTW: Inverse probability of treatment weighting; OR: Odds ratio

Table 2.2. Number, Percent, and Weighted Percent of Patient-level Characteristics by Presence of Cancer

Characteristics	Before IPTW				Sig	After IPTW		Sig
	Cancer cohort		Non-cancer cohort			Cancer cohort	Non-cancer cohort	
	N	%	N	%		Wt. %	Wt. %	
Age groups					***			NS
68-70 years	1,983	16.4	6,860	16.0		16.0	16.1	
71-74 years	2,887	23.9	8,186	19.1		19.8	20.1	
75-79 years	3,158	26.1	9,423	22.0		22.8	22.9	
80 years and older	4,068	33.6	18,336	42.8		41.5	40.9	
Sex					***			NS
Female	5,712	47.2	26,764	62.5		59.4	59.2	
Male	6,384	52.8	16,041	37.5		40.6	40.8	
Race/Ethnicity								NS
Whites	9,928	82.1	33,308	77.8	***	78.8	78.8	
African Americans	1,013	8.4	3,538	8.3		8.2	8.3	
Hispanics	319	2.6	1,687	3.9		3.7	3.7	
Others	836	6.8	4,272	10.0		9.3	9.3	
SEER Region					***			NS
Northeast	2,749	22.7	9,021	21.1		21.5	21.4	
South	2,977	24.6	10,963	25.6		25.3	25.4	
North-central	1,691	14	5,029	11.7		12.2	12.2	
West	4,679	38.7	17,792	41.6		41	40.9	
Index year					*			NS
2008	2,966	24.5	10,001	23.4		23.2	23.6	
2009	2,975	24.6	10,480	24.5		24.5	24.5	
2010	2,992	24.7	11,133	26.0		26	25.8	
2011	3,163	26.1	11,191	26.1		26.3	26.1	

Asterisks represent significant differences in time-invariant patient-level characteristics based on chi-square tests

***p < 0.001; **0.001 ≤ p < 0.01; *0.01 ≤ p < 0.05. Column percentages are reported.

Abbreviations

ACEI: Angiotensin-converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; CAD: Coronary artery disease; IPTW: inverse probability treatment weighting; Sig: Significance

2.4.2 Unadjusted and Adjusted Relationship between Cancer and Adherence to Statins and/or ACEIs/ARBs/Beta-blockers

Table 2.3 summarizes the number and weighted percentage of medication adherence categories among cancer and non-cancer cohorts. Overall, only 29.1% were adherent to both statins and ACEIs, ARBs, or beta-blockers and 14.6% were not adherent to both of these medication classes. Even among those with single medication class, 14.7% were not adherent. **Table 2.3** also displays the odds ratios and 95% confidence intervals (CI) from the *unadjusted* GEE models on adherence. The significance of the association was derived from the unadjusted GEE models. The reference group for the dependent variable was “adherence to both statins and ACEIs/ARBs/beta-blockers”. For ease of interpretation, we summarize the findings by cancer and no cancer differences, sex differences, and cancer type differences in adherence.

2.4.2.1 Cancer versus No Cancer and Medication Adherence

CCW were less likely to be adherent to both statins and ACEIs/ARBs/beta-blockers compared to NCW [OR = 0.72; 95% CI = 0.61; 0.83, $P < 0.001$]. However, BCW were more likely to be adherent to both medication classes compared to NCW [OR = 1.09; 95% CI = 1.01, 1.17; $P < 0.05$]. Similarly, CCM were less likely to be adherent to both medication classes compared to NCM [OR = 0.66; 95% CI = 0.55, 0.78; $P < 0.001$]. PCM were less likely to be adherent to both medication classes compared to NCM [OR = 0.92; 95% CI = 0.85; 0.99, $P = 0.026$]. Among those with single medication use, similar patterns were observed.

2.4.2.2 Sex and Medication Adherence

We compared NCW to NCM and CCW to CCM to infer sex differences in adherence categories. There were no significant differences in adherence to both medication classes by sex in the unadjusted. However, NCW [AOR = 1.10; 95% CI = 1.06, 1.14] and CCW [AOR = 1.21; 95% CI = 1.08, 1.34] were more likely to be either adherent to one (out of two) medication class or adherent to one medication class among those with one medication class compared to NCM and CCM respectively.

Table 2.3. Weighted Percent and Unadjusted GEE Models with IPTW on Medication Adherence Categories

Characteristics	ADH 2 Rx (Weighted %) N = 80,957	No ADH 2 Rx (Weighted %) N = 41,016	ADH 1 of 2 Rx (Weighted %) N = 60,167	ADH 1 Rx (Weighted %) N = 55,536	No ADH 1 Rx (Weighted %) N = 40,500
All	29.1%	14.7%	21.6%	20.0%	14.6%
Cancer and No Cancer Categories					
BCW	28.7	13.3	22.2	21.2	14.6
CCW	24.5	16.9	23.5	18.7	16.4
NCW	27.3	13.9	21	22.7	15.2
CCM	27.3	19.6	23	13.9	16.2
PCM	31.5	16.5	23.2	15.6	13.2
NCM	32.1	15.3	21.6	17.4	13.6
OR [95% CI] Reference group OR [95% CI] OR [95% CI] OR [95% CI]					
Cancer vs no cancer differences in adherence (Reference: NCW)					
BCW	1.10 [1.02,1.18]*		1.10 [1.03,1.17]**	0.97 [0.88,1.07]	1.00 [0.90,1.10]
CCW	0.73 [0.61,0.84]***		0.91 [0.81,1.01]	0.67 [0.53,0.81]***	0.88 [0.74,1.03]
CCM	0.69 [0.58,0.81]***		0.77 [0.67,0.87]***	0.42 [0.26,0.58]***	0.75 [0.59,0.90]***
PCM	0.96 [0.90,1.03]		0.93 [0.86,0.99]*	0.57 [0.48,0.66]***	0.73 [0.63,0.82]***
NCM	1.06 [0.99,1.11]		0.93 [0.89,0.98]**	0.69 [0.63,0.76]***	0.81 [0.75,0.88]***
Cancer vs no cancer differences in adherence (Reference: NCM)					
BCW	1.03 [0.95,1.11]		1.18 [1.11,1.26]***	1.40 [1.30,1.50]***	1.23 [1.12,1.34]***
CCW	0.68 [0.57,0.80]***		0.98 [0.88,1.08]	0.96 [0.82,1.11]	1.09 [0.94,1.23]
CCM	0.65 [0.53,0.77]***		0.82 [0.72,0.92]***	0.61 [0.45,0.77]***	0.92 [0.76,1.08]***
PCM	0.91 [0.84,0.98]**		0.99 [0.93,1.06]	0.83 [0.73,0.92]***	0.90 [0.80,1.00]
NCW	0.94 [0.89,1.00]		1.07 [1.03,1.12]**	1.44 [1.38,1.50]***	1.23 [1.17,1.30]*
Sex Differences in adherence (other categories not displayed)[†]					
NCW	0.94 [0.89,1.00]		1.07 [1.03,1.12]**	1.44 [1.38,1.50]***	1.23 [1.17,1.30]*
NCM	Reference				
CCW	1.05 [0.89,1.20]		1.19 [1.05,1.32]*	1.58 [1.37,1.78]***	1.18 [0.98,1.39]
CCM	Reference				
Cancer Type Differences in adherence (other categories not displayed)[‡]					
BCW	1.51 [1.38,1.64]***		1.21 [1.10,1.32]**	1.46 [1.30,1.62]***	1.13 [0.97,1.30]
CCW	Reference				
PCM	1.40 [1.27,1.52]***		1.21 [1.10,1.32]***	1.35 [1.18,1.53]***	0.97 [0.80,1.15]
CCM	Reference				

The analysis was based on 6 repeated measures.

[†]Other categories not displayed are: BCW and PCM. [‡]Other categories not displayed are: NCW and NCM.

Description of medication use and adherence

ADH 2 Rx: Adherent to both medication classes (statins and ACEIs/ARBs/beta-blockers)

No ADH 2 Rx: Not adherent to both medication classes (**reference**)

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers

ADH 1 Rx: Use of one medication class (either statins or ACEIs/ARBs/beta-blockers) and adherent to that class

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in cancer diagnosis categories, derived from GEE, which accounts for repeated observations

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

Abbreviations

BCW: Women with breast cancer women; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; GEE: Generalized estimating equations;

IPTW: Inverse probability of treatment weighting; NCM: Men with no cancer; NCW: Women with no cancer; PCM: Men with prostate cancer

2.4.2.3 Cancer Type and Medication Adherence

BCW were more likely to be adherent to both [OR = 1.51; 95% CI = 1.38, 1.64; $P < 0.001$] medication classes compared to CCW. PCM were more likely to be adherent to both medication classes compared to CCM [OR = 1.39; 95% CI = 1.27, 1.52; $P < 0.001$]. Among those with single medication use, similar patterns were observed.

Table 2.4 displays the adjusted odds ratios (AORs) and 95% CI from the *adjusted* GEE regressions on adherence categories. The findings were similar to unadjusted models. For example, CCW were less likely to be adherent to both classes of medications compared to NCW [AOR = 0.70; 95% CI = 0.58, 0.81; $P < 0.0001$]. Similarly, CCM [AOR = 0.63; 95% CI = 0.51, 0.75; $P < 0.0001$] and PCM [AOR = 0.92; 95% CI = 0.85, 0.99; $P = 0.022$] were less likely to be adherent to both classes of medications compared to NCM.

However, there was no significant differences observed in any of the adherence categories between BCW compared to NCW, after controlling for other factors. This is in contrast to unadjusted model, in which, there was significant difference between BCW as compared to NCW.

Table 2.5 displays the AORs and 95% CI from the adjusted GEE models on adherence for other independent variables. Medicare beneficiaries who were < 80 years, Whites, had no concordant physical health conditions, had discordant physical health conditions, had mental health conditions, had tobacco and alcohol use, and had no cardiologist visit were less likely to be adherent to both medication classes

2.4.3 Secondary Analyses

As CCW and CCM were generally non-adherent to medications, we further examined the relationship between cancer-related factors (stage of diagnosis and cancer treatment (surgery, chemo, radiation therapies) among men and women with CAD and incident colorectal cancer (CC) (**Table 2.6**). These analyses indicated that those with advanced cancer stage were less likely to be adherent to both medication classes (AOR = 0.55; 95% CI = 0.31, 0.78) compared to early-stage cancer. Similarly, those who had surgery were less likely to be adherent to both medication classes (AOR = 0.64; 95% CI = 0.45, 0.82).

Table 2.4. Adjusted GEE Models with IPTW on Adherence to Medication Adherence Categories

Sex and cancer categories	ADH 2 Rx			ADH 1 Rx of 2			ADH 1 Rx			No ADH 1 Rx		
	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig
Cancer vs no cancer differences in adherence (Reference = NCW)												
BCW	1.08	[1.00,1.17]		1.08	[1.00,1.15]		1.03	[0.93,1.13]		1.06	[0.96,1.17]	
CCW	0.70	[0.58,0.81]	***	0.87	[0.77,0.97]	**	0.65	[0.51,0.80]	***	0.91	[0.76,1.05]	
CCM	0.63	[0.51,0.75]	***	0.71	[0.61,0.82]	***	0.46	[0.30,0.63]	***	0.85	[0.70,1.01]	
PCM	0.92	[0.85,0.99]	*	0.89	[0.82,0.95]	***	0.68	[0.59,0.78]	***	0.86	[0.76,0.96]	**
NCM	1.02	[0.97,1.07]		0.91	[0.86,0.96]	***	0.78	[0.71,0.84]	***	0.89	[0.82,0.96]	**
NCW	Reference											
Cancer vs no cancer differences in adherence (Reference = NCM)												
BCW	1.06	[0.98,1.15]		1.18	[1.11,1.26]	***	1.32	[1.22,1.43]	***	1.19	[1.08,1.30]	**
CCW	0.68	[0.56,0.80]	***	0.96	[0.86,1.07]		0.84	[0.69,0.99]	*	1.02	[0.87,1.17]	
CCM	0.62	[0.49,0.74]	***	0.78	[0.68,0.89]	***	0.59	[0.42,0.76]	***	0.96	[0.80,1.12]	
PCM	0.90	[0.83,0.98]	**	0.98	[0.91,1.04]		0.88	[0.78,0.98]	*	0.96	[0.86,1.07]	
NCW	0.98	[0.93,1.03]		1.10	[1.05,1.15]	***	1.29	[1.22,1.36]	***	1.12	[1.05,1.19]	**
NCM	Reference											
Sex Differences in adherence (other categories not displayed) [†]												
NCW	0.98	[0.93,1.03]		1.10	[1.05,1.15]	***	1.29	[1.22,1.36]	***	1.12	[1.05,1.19]	**
NCM	Reference											
CCW	1.11	[0.95,1.27]		1.23	[1.09,1.36]	**	1.41	[1.20,1.63]	**	1.06	[0.85,1.27]	
CCM	Reference											
Cancer Type Differences in adherence (other categories not displayed) [‡]												
BCW	1.55	[1.42,1.69]	***	1.23	[1.11,1.35]	***	1.57	[1.40,1.74]	***	1.17	[1.00,1.34]	
CCW	Reference											
PCM	1.46	[1.33,1.60]	***	1.24	[1.13,1.36]	***	1.48	[1.30,1.66]	***	1.01	[0.83,1.18]	
CCM	Reference											

[†]Other categories not displayed include BCW and PCM. [‡]Other categories not displayed include NCW and NCM.

Description of medication use and adherence

ADH 2 Rx: Adherent to both medication classes (statins and ACEIs/ARBs/beta-blockers)

No ADH 2 Rx: Not adherent to both medication classes (**reference**)

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers

ADH 1 Rx: Use of one medication class (either statins or ACEIs/ARBs/beta-blockers) and adherent to that class

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in cancer diagnosis categories, derived from GEE, which accounts for repeated observations. Adjusted GEE model controlled for patient, physician, health-system, and environmental factors.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

Abbreviations

AOR: Adjusted odds ratio; BCW: Women with breast cancer; CAD: Coronary artery disease; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; CI: Confidence interval; GEE: Generalized estimating equations; IPTW: Inverse probability of treatment weighting; NCM: Men with no cancer; Women with no cancer; PCM: Men with prostate cancer; Sig: Significance

Table 2.5. Adjusted GEE Models with IPTW on Medication Adherence Categories—Other factors included based on conceptual framework

Characteristics	ADH 2 Rx			ADH 1 of 2 Rx			ADH 1 Rx			No ADH 1 Rx		
	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig
Patient-level factors - Demographics												
Age groups (in years)												
68-70	0.94	[0.88,1.00]		0.98	[0.92,1.03]		0.55	[0.47,0.63]	***	0.67	[0.59,0.76]	***
71-74	0.90	[0.84,0.96]	***	0.98	[0.92,1.03]		0.58	[0.50,0.65]	***	0.66	[0.58,0.74]	***
75-79	0.95	[0.90,1.01]		1.01	[0.96,1.06]		0.68	[0.61,0.75]	***	0.76	[0.69,0.84]	***
≥80		Reference			-			-			-	
Race/Ethnicity												
African Americans	0.63	[0.55,0.72]	***	0.78	[0.71,0.85]	***	0.75	[0.65,0.85]	***	1.04	[0.95,1.14]	
Hispanics	0.59	[0.47,0.71]	***	0.74	[0.63,0.84]	***	0.61	[0.46,0.76]	***	0.85	[0.71,1.00]	*
Others	0.90	[0.83,0.98]	*	0.87	[0.80,0.94]	***	0.83	[0.73,0.93]	***	0.89	[0.79,1.00]	*
Whites		Reference										
Patient-level factors - Census-tract socioeconomic status												
Education level												
<12% (national avg)	1.01	[0.96,1.07]		0.99	[0.95,1.04]		1.00	[0.94,1.07]		1.05	[0.98,1.11]	
≥12% (national avg)		Reference			-			-			-	
Poverty level												
<14.3% (national avg)	1.03	[0.98,1.08]		1.06	[1.02,1.11]	**	1.11	[1.04,1.17]	**	1.10	[1.04,1.16]	**
≥ 14.3% (national avg)		Reference			-			-			-	
Patient-level factors - Chronic physical and mental health conditions												
Concordant PHCs												
Yes	1.40	[1.29,1.50]	***	1.40	[1.31,1.50]	***	0.70	[0.59,0.81]	***	0.48	[0.37,0.60]	***
No		Reference			-			-			-	
Discordant PHCs												
Yes	0.78	[0.73,0.83]	***	0.88	[0.84,0.92]	***	1.12	[1.06,1.17]	***	1.27	[1.22,1.33]	***
No		Reference			-			-			-	
Mental health conditions												
Yes	0.66	[0.60,0.71]	***	0.77	[0.72,0.82]	***	0.88	[0.82,0.95]	***	1.08	[1.02,1.15]	*
No		Reference			-			-			-	
CAD severity	1.02	[0.91,1.13]		1.05	[0.95,1.15]		0.57	[0.42,0.71]	***	0.63	[0.49,0.78]	***
Patient-level factors - Personal health behavior												
Tobacco use												
Yes	1.32	[1.21,1.43]	***	1.22	[1.13,1.31]	***	1.44	[1.30,1.58]	***	1.14	[1.01,1.28]	
No		Reference			-			-			-	
Alcohol use												
Yes	1.48	[1.27,1.69]	***	1.28	[1.10,1.46]	**	1.00	[0.74,1.26]		0.63	[0.39,0.87]	***
No		Reference			-			-			-	

Characteristics	ADH 2 Rx			ADH 1 of 2 Rx			ADH 1 Rx			No ADH 1 Rx		
	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig
Health System Factors												
Donut hole												
Exceeded	0.96	[0.87,1.05]		0.99	[0.89,1.09]		1.00	[0.91,1.10]		0.99	[0.88,1.10]	
Not reached	0.35	[0.26,0.43]	***	0.59	[0.51,0.68]	***	0.66	[0.56,0.77]	***	1.32	[1.20,1.44]	***
Reached	Reference			-			-			-		
Provider Related Factors												
Primary care visit												
Yes	1.01	[0.97,1.05]		1.08	[1.04,1.11]	***	0.95	[0.91,1.00]		0.96	[0.91,1.01]	
No	Reference			-			-			-		
Cardiologist visit												
Yes	1.04	[1.01,1.07]	*	1.12	[1.09,1.15]	***	0.69	[0.65,0.73]	***	0.70	[0.66,0.74]	***
No	Reference			-			-			-		
External Environment and County-level Factors												
SEER Region												
Northeast	1.07	[1.00,1.15]		1.05	[0.99,1.12]		1.07	[0.97,1.16]		0.94	[0.84,1.03]	
South	0.96	[0.89,1.04]		1.05	[0.99,1.12]		0.98	[0.88,1.07]		1.02	[0.92,1.12]	
North-central	1.17	[1.09,1.25]	***	1.08	[1.01,1.15]	*	1.14	[1.04,1.24]	**	0.94	[0.84,1.05]	
West	Reference			-			-			-		
Metropolitan status												
Metro	0.92	[0.84,0.99]	*	0.94	[0.87,1.00]	*	0.89	[0.80,0.98]	*	1.00	[0.91,1.10]	
Non-metro	Reference			-			-			-		
HPSA												
No shortage	1.07	[0.98,1.15]		1.04	[0.96,1.12]		1.03	[0.92,1.13]		0.95	[0.83,1.06]	
Part county	1.07	[1.01,1.12]	*	1.03	[0.99,1.08]		1.02	[0.96,1.09]		1.04	[0.97,1.11]	
Whole county	Reference			-			-			-		
FQHC												
None	1.15	[1.05,1.26]	**	1.04	[0.95,1.13]		1.14	[1.01,1.26]		1.03	[0.90,1.16]	
1 to 10	1.05	[0.98,1.11]		0.99	[0.94,1.05]		1.10	[1.02,1.18]	*	1.05	[0.97,1.14]	
≥11	Reference			-			-			-		
Rural health centers												
Yes	1.02	[0.97,1.08]		0.99	[0.94,1.05]		1.02	[0.95,1.09]		1.03	[0.96,1.10]	
No	Reference			-			-			-		
% cardiologists in county	0.84	[0.75,0.93]	***	0.92	[0.84,1.00]	*	1.08	[0.96,1.19]		1.14	[1.02,1.25]	*
% oncologists in county	2.23	[1.79,2.68]	***	1.37	[0.99,1.76]		0.68	[0.13,1.24]		0.55	[0.02,1.12]	*
Time	1.41	[1.40,1.41]	***	1.26	[1.25,1.26]	***	1.35	[1.35,1.36]	***	1.12	[1.12,1.13]	***

Time-invariant characteristics include cancer diagnosis categories, age, race/ethnicity, poverty status, high school education, concordant and discordant physical health conditions, SMI, SEER region, and county-level characteristics. Time-variant characteristics include, tobacco use, alcohol use, depression, anxiety, and routine follow-up with primary care physician and/or cardiologist, and donut hole.

Concordant physical health conditions consisted of diabetes, hyperlipidemia, hypertension, stroke, cardiac arrhythmia, and congestive heart failure. Discordant physical health conditions consisted of arthritis, asthma, chronic obstructive pulmonary disease, osteoporosis, dementia, human immunodeficiency virus, and hepatitis. Mental health conditions include anxiety, depression, SMI (schizophrenia, bipolar disorder, and psychoses)

Description of medication use and adherence

ADH 2 Rx: Adherent to both medication classes (statins and ACEIs/ARBs/beta-blockers)

No ADH 2 Rx: Not adherent to both medication classes (**reference**)

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers

ADH 1 Rx: Use of one medication class (either statins or ACEIs/ARBs/beta-blockers) and adherent to that class

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in cancer diagnosis categories, derived from GEE, which accounts for repeated observations.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

Abbreviations

AOR: Adjusted odds ratio; CI: Confidence interval; FQHC: Federally qualified health centers; GEE: Generalized estimating equations; HPSA: Health professional shortage area; IPTW: inverse probability treatment weights; PHC: Physical health condition; Sig: Significance; SMI: Severe mental illness

Table 2.6. Adjusted GEE models on Medication Adherence Categories among Patients with Colorectal Cancer (N = 3,104)

Characteristics	ADH 2 Rx			ADH 1 of 2 Rx			ADH 1 Rx			No ADH 1 Rx		
	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig
Cancer stage												
Stage II	0.77	[0.54,0.99]	*	0.82	[0.61,1.02]		1.09	[0.82,1.35]		1.21	[0.94,1.48]	
Stage III/IV	0.55	[0.31,0.78]	***	0.63	[0.41,0.84]	***	0.72	[0.43,1.00]	*	0.84	[0.56,1.13]	
Stage 0/I		Reference										
Surgery												
Yes	0.64	[0.45,0.82]	***	0.72	[0.53,0.91]	***	0.66	[0.47,0.85]	***	0.96	[0.76,1.16]	
No		Reference										
Chemotherapy												
Yes	1.03	[0.77,1.28]		1.25	[1.02,1.49]		0.97	[0.66,1.27]		1.32	[1.03,1.62]	
No		Reference										
Radiation therapy												
Yes	0.91	[0.54,1.29]		0.89	[0.52,1.26]		0.74	[0.28,1.19]		0.82	[0.38,1.26]	
No		Reference										
Hormone therapy												
Yes	0.87	[0.28,1.42]		0.52	[0.32,1.55]		1.24	[0.80,1.55]		0.42	[0.23,1.57]	
No		Reference										

Description of medication use and adherence

ADH 2 Rx: Adherent to both medication classes (statins and ACEIs/ARBs/beta-blockers)

No ADH 2 Rx: Not adherent to both medication classes (**reference**)

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers

ADH 1 Rx: Use of one medication class (either statins or ACEIs/ARBs/beta-blockers) and adherent to that class

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in cancer diagnosis categories, derived from GEE models, which controlled for patient, physician, health-system, and environmental factors.

***p < 0.001; **0.001 ≤ p < 0.01; *0.01 ≤ p < 0.05.

Abbreviations

AOR: Adjusted odds ratio; CI: Confidence interval; GEE: Generalized estimating equations; Sig: Significance

2.5 Discussion

The current study analyzed the relationship between incident cancer diagnosis and adherence to statins and/or ACEIs/ARBs/beta-blockers among elderly FFS Medicare beneficiaries with pre-existing CAD. To the best of our knowledge, this is the first study to compare medication adherence to statins and/or ACEIs/ARBs/beta-blockers between cancer and non-cancer cohorts with CAD. In general, only 28.9% of the study population were adherent to both statins and ACEIs/ARBs/beta blockers. Although there are no published studies comparing cancer and non-cancer patients, our figures are similar to existing studies on medication adherence to multiple medication classes in those with cardiovascular conditions. Given that there is dearth of studies in the area of multiple medication adherence among those with CAD, specifically among those with elderly, it is important to learn from published studies in cardiovascular conditions. One study showed that 21.4% adults with cardiovascular conditions were adherent to both statins and calcium channel blockers [159]. Similarly, another study reported that 21% had combined adherence on beta-blockers, lipid lowering therapy, and aspirin [160].

These findings emphasize the need for multimodal interventions for improving medication adherence. Ho et al reviewed studies on medication adherence among individuals with cardiovascular health conditions and suggested that multimodal interventions including the pharmacist-led interventions may be successful in realizing the benefits of medication adherence and reducing the costs of non-adherence [141]. Future studies need to examine whether the proven strategies of medication adherence can also be applied to improve medication adherence of multiple drug regimens.

We observed that both men and women diagnosed with incident colorectal cancer were less likely to adhere to both statins and ACEIs/ARBs/beta-blockers compared to non-cancer women and men, even after controlling for a comprehensive list of factors. Similarly, men with incident prostate cancer were less likely to adhere to both medication classes, but the magnitude of difference was much less compared to men with no cancer diagnosis. There were no differences in adherence to both medication classes by presence of breast cancer. Taken together, these findings suggest that cancer type rather than cancer itself may affect medication adherence. Furthermore, we also found that among Medicare beneficiaries with CAD and colorectal cancer, those with late-stage cancer compared to early stage cancer and those who had surgical treatment for cancer compared to no surgical treatment were less likely to be adherent to both statins and ACEIs/ARBs/beta blockers. These findings suggest that cancer stage and cancer treatment may affect medication adherence among colorectal cancer patients. It is also plausible that the life-threatening nature of CC may lead to prioritization of cancer care. For example, colorectal cancer has lower 5-year survival rates compared to breast and prostate cancer (66% vs. 91% and 99%, respectively) [106].

Despite the complexity of care among those with multiple chronic conditions (in our case those with CAD and CC), it is important to focus on medication adherence for CAD. However, under the fee-for-service programs, there are no incentives to coordinate care across multiple systems, providers, and payers [141]. In this context, the new fiscal incentives by the CMS in paying physicians who provide care for patients with multiple chronic conditions and who invest time and resources to provide more coordinated and patient-centered care [161] may also promote adherence. It has to be noted that a systematic review of medication adherence among those with multiple chronic conditions reported that medication adherence interventions were “almost exclusively” conducted by the

pharmacists [162]. In recognition of the critical role of pharmacists, Medicare now covers Medication Management Services (MTM) of pharmacists. There is some evidence that such policies (i.e. MTM services offered by pharmacists) can improve adherence and lead to better cardiovascular outcomes [163].

2.5.1 Clinical Implications

Our study findings have implications for clinical practice. As mentioned in the introduction, statins and ACEIs/ARBs/beta-blockers are central to improving CAD-related health outcomes and statins have been shown to reduce cancer-specific mortality in those with breast, colorectal, and prostate cancer [144-146, 164]. Furthermore, medications for CAD may also reduce cancer treatment-related cardiotoxicity [71]. We do recognize that medication adherence is a multidimensional issue in which providers, patients, payers, and policy makers are inextricably linked and all of them need to be involved in improving medication adherence [165]. It may be very challenging for clinicians to implement interventions in routine practice because successful to date have included multiple, heterogeneous components [141]. In this context, the recent healthcare delivery models such as the medical home may help in overcoming the challenges to coordination across different providers. It has been shown that patient-centered medical homes can improve adherence to medications among those with cardiovascular conditions [166].

2.5.2 Strengths and Limitations

Our study findings need to be interpreted in the context of its limitations. The study findings cannot be generalized to all Medicare beneficiaries because the study population is restricted to those residing in SEER regions and to those with FFS Medicare plans. Although we used a proxy measure for CAD severity, this measure may not accurately capture severity of the disease. We were not able to control for patient-level lifestyle health behaviors, knowledge, attitude, and preferences as well as number of cancer-related complications, treatment side-effects, and cost-related factors that may affect adherence. We used prescription claims for measuring adherence. As part D file contains only filled prescriptions, it is not known whether the patient actually used the medications or whether the patients they adhered to their providers' instructions or not. The focus of the study was only on statins and ACEIs/ARBs/beta-blockers, as they are recommended by guidelines for CAD long-term therapy. Substitution with any other drugs other than those included in the study are considered non-users of the respective medication. This does not affect adherence as those drugs are not recommended by guidelines for long-term CAD pharmacotherapy.

Our study has many advantages. The study used a rigorous study design comparing cancer and non-cancer cohort over time and statistical adjustment for selection bias in observed characteristics. Medicare FFS claims data enabled us to measure adherence over time and followed a large cohort of patients for a long period of time across a variety of providers. The study adjusted a comprehensive list of factors that can influence medication adherence. The study included individuals with significant medical comorbidities, typically excluded from randomized clinical trials and examined real-world practice patterns.

2.5.3 Conclusions

The findings from our study contribute to existing literature on adherence and adds to the nascent field of cardio-oncology. We observed that medication adherence was associated with cancer type rather than just the presence of cancer itself. Elderly Medicare beneficiaries with colorectal cancer and to a lesser extent men with prostate cancer were less likely to be adherent to evidence-based medications for CAD. These findings highlight the vulnerability of these individuals and the difficulty in sustaining ongoing therapy for CAD. The recent healthcare delivery models such as the medical home may help in overcoming the challenges to coordination across different providers and can improve adherence to medications among those with cardiovascular conditions.

CHAPTER 3

Non-adherence to Statins and Antihypertensive Medications and Hospitalizations among Elderly Fee-for-Service Medicare Beneficiaries with Pre-existing Coronary Artery Disease and Incident Cancer

3.1 Abstract

Objectives: To examine the relationship between adherence to both statins and ACEIs/ARBs/beta-blockers and coronary artery disease (CAD)-related hospitalizations.

Methods: A retrospective observational longitudinal study was conducted using SEER-Medicare data. Elderly Medicare fee-for-service beneficiaries with pre-existing CAD and incident breast, colorectal, or prostate cancer (N = 12,096) were observed for a period of 12 months before and 12 months after cancer diagnosis. Hospitalizations measured every 120-days were categorized into three groups: (1) any CAD-related hospitalization; (2) other hospitalizations; or (3) no hospitalization. Medication adherence was categorized into five mutually exclusive groups: (1) adherent to both statins and ACEIs/ARBs/beta-blockers (reference group); (2) not adherent to both statins and ACEIs/ARBs/beta-blockers; (3) adherent to either statins or ACEIs/ARBs/beta-blockers; (4) use of one medication class and adherent to that class; or (5) use of one medication class and not adherent to that medication class. The unadjusted and adjusted relationship between medication adherence and hospitalization was analyzed using repeated measures multinomial logistic regressions. Inverse probability treatment weights were used to control for observed group differences among medication adherence categories.

Results: Adherence to both statins and ACEIs/ARBs/beta-blockers was estimated at 31.2% during the 120-day period immediately after cancer diagnosis; 13.7% were not adherent to both medication classes during the same period; 27.4% had CAD-related hospitalizations immediately after cancer diagnosis and this percentage declined to 10.6% during the last four months of the post-cancer period. In the adjusted analyses, those not adherent to both statins and ACEIs/ARBs/beta-blockers were more likely to have CAD-related hospitalization compared to those who were adherent to both medication classes [AOR = 1.82; 95% CI = 1.72, 1.92; $P < 0.0001$].

Conclusions: Given the complexity of interaction between CAD and cancer, it is important to routinely monitor medication adherence in general clinical practice and provide linkages to support services that can increase medication adherence.

3.2 Introduction

Coronary artery disease (CAD) remains the leading cause of hospitalization in the United States (US), although the rate of hospitalization for CAD has declined from 77% in 2000 to 44% in 2010 [167]. According to the Healthcare Cost and Utilization Project (HCUP), in 2010, CAD accounted for nearly 512,000 hospital admissions with an estimated inpatient expenditures of nearly \$9.5 billion [168]. Among individuals with CAD, per-capita hospital expenditures were estimated at \$22,700 in 2014 accounting for about 62% of total direct medical care expenditures [4, 169], suggesting that hospitalizations are the primary drivers of total direct medical care expenditures.

Existing evidence also suggests that adults, especially older individuals (age > 65 years) with incident cancer may be at risk for non-cancer related hospitalizations. Although not specific to CAD-related hospitalizations, men with incident prostate cancer and cardio-metabolic conditions were more likely to experience hospitalization during the immediate period after cancer diagnosis [170]. It has been reported that the risk of first hospitalization for CAD increases during the six months after cancer diagnosis [171], perhaps due to cardiotoxicity associated with cancer treatments such as radiotherapy, chemotherapy, and hormone therapy [60-62]. Some studies have reported increased risk of cardiovascular events, complications, and mortality in women who were treated with radiotherapy [172-174] or were exposed to cardiotoxic drugs (trastuzumab and anthracycline) [108, 175, 176]. Similarly, endocrine treatment-related cardiotoxicity has also been reported in prostate cancer patients [177-179].

Adherence to angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-blockers, and statins have been shown to not only improve survival [95, 131] but also reduce the risk of CAD-related hospitalizations [94, 95]. Specifically, statins have been reported to reduce cancer-specific mortality in those with breast, colorectal, and prostate cancer [144-146, 164], suggesting that adherence to statins may be even more important for individuals with cancer.

However, to date, no study has examined the relationship between adherence to statins and ACEIs/ARBs/beta-blockers, and CAD-related hospitalization in older individuals (age > 65 years) with pre-existing CAD and incident cancer. As old age is a risk factor for CAD-related hospitalization [168] and CAD is the most common pre-existing condition among older adults diagnosed with cancer [85, 86, 90], it is important to analyze the relationship between adherence to both statins and ACEIs/ARBs/beta-blockers and CAD-related hospitalizations among cancer patients. Therefore, the present study evaluated the relationship between adherence to both statins and ACEIs/ARBs/beta-blockers and CAD-related hospitalizations among elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal or prostate cancer, after controlling for cancer treatment that are cardiotoxic and other risk factors that may affect CAD-related hospitalizations.

3.3 Methods

3.3.1 Conceptual Framework

This study adapted Andersen's Behavioral Model of health service utilization to select independent variables that may influence CAD-related hospitalizations (**Figure 1.2**) [124, 125]. This model categorizes variables that may influence CAD-related hospitalization into predisposing (age, sex, race), enabling (census tract education level and

poverty status, marital status, Medicare prescription drug coverage), need factors (chronic physical and mental health conditions, cancer type, cancer stage, cancer treatment), personal health practices (tobacco and alcohol use), healthcare use (visits to primary care/cardiologist and adherence to statins and/or ACEIs/ARBs/beta-blockers) and external environment (Surveillance, Epidemiology and End Results [SEER] region and county metro status).

3.3.2 Study Design

The study utilized a retrospective observational longitudinal cohort design with baseline (24-36 months before cancer diagnosis), pre-cancer (12 months before cancer diagnosis) and post-cancer (12 months after cancer diagnosis) periods (**Figure 3.1**).

Figure 3.1. Schematic presentation of study design

3.3.3 Data Sources

We linked data from four sources: the SEER registries, Medicare claims, the American Community Survey (ACS), and the Area Health Resource Files (AHRF). SEER program is an epidemiologic surveillance system consisting of population-based tumor registries that collects data on all incident cases of cancer that occur in persons residing in 18 SEER areas. SEER data also consists of information about demographic characteristics of the patient, diagnosis date, cancer site, stage, and grade [126]. The ACS census tract files provided information on the census tract poverty status [128]. The AHRF was used to derive percent cardiologists and oncologists in the county [129].

3.3.4 Study Population

Individuals with CAD were identified using a validated algorithm developed by the Centers for Medicare and Medicaid Services (CMS) [150]. The algorithm used the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes. Individuals with at least one inpatient or two outpatient claims (institutional outpatient, physician office, and home health agency claims) with a primary or secondary diagnosis of CAD during the baseline were classified as having pre-existing CAD. Individuals with incident cancer, were identified from the SEER registry for the period between January 2008 and December 2011.

Other inclusion criteria were: (1) age 68 years or older at cancer diagnosis; (2) no missing data for type and stage of cancer; (3) alive with continuous FFS Medicare Part A, B enrollment during the entire study period; (4) continuous part D enrollment during the pre- and post-index period; (5) no missing information on county, and (6) having two or more prescriptions for either statins or two or more prescriptions for any one of the following

medication types: ACEIs, ARBs, or beta-blockers. Those who were diagnosed with cancer through autopsy or death certificate were also excluded. The selection criteria are presented in **Figure 3.2**

3.3.5 Measures

3.3.5.1 Dependent Variable: Any Hospitalization for CAD Events

The dependent variable was categorized into three mutually exclusive groups based on a hierarchy: (1) any CAD-related hospitalization; (2) other hospitalization (hospitalizations other than CAD); and (3) no hospitalization. CAD-related hospitalizations were defined as inpatient admissions for any cardiovascular event (heart attack, heart failure, angina, or stroke) and were identified from primary and secondary diagnoses using ICD-9-CM codes [180]. This measure was calculated during 120-days before cancer-diagnosis and every 120-days during the post-cancer period. A 120-day interval before cancer diagnosis was a baseline measurement to ensure that the change in hospitalization was associated with adherence and not due to any other factors.

3.3.5.2 Key Independent Variable: Adherence to Statins, ACEIs/ARB/Beta-blockers

This measure was also calculated for 120-days before cancer-diagnosis and every 120-days during the post-cancer period. A 120-day interval before cancer diagnosis was a baseline measurement to account for change in adherence due to cancer diagnosis. Based on the type of drug regimen and individuals were classified into five mutually exclusive groups: (1) adherent to both statins and ACEIs/ARBs/beta-blockers; (2) not adherent to both statins and ACEIs/ARBs/beta-blockers; (3) adherent to either statins or ACEIs/ARBs/beta-blockers; (4) use of one medication class and adherent to that class; and (5) use of one medication class and not adherent to that medication class.

Statins, ACEIs, ARBs, and beta-blockers were identified using the generic names in the Part D event files.

Proportion of days covered (PDC) was used to measure adherence to statins, ACEIs, ARBs, or beta-blockers and was calculated for those who filled at least two prescriptions for either statins or two prescriptions for ACEIs, ARBs, or beta-blockers. The PDC was calculated as: $\frac{\text{Days of medication supplied during each time period } (t_0, t_1, t_2, t_3)}{\text{Days in each time period (120 days)}}$. For those

with a drug regimen (i.e. statins and ACEIs, ARBs or beta-blockers), PDC includes days within a specific period when an individual is covered for both statins and beta-blockers, ACEIs, or ARBs. PDC was dichotomized, where individuals with $\text{PDC} \geq 80\%$ were considered as adherent and those with $\text{PDC} < 80\%$ as non-adherent [153].

Figure 3.2. Schematic presentation of selection criteria for study cohort.

Abbreviations – ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; BB: Beta-blockers; CAD: Coronary artery disease; HMO: Health Maintenance Organization; R_x: Prescription

3.3.5.3 Other Independent Variables

Predisposing Factors

These were time-invariant and comprised age in years measured at index month of incident cancer diagnosis, sex, and race/ethnicity.

Enabling Factors

These factors included marital status (measured at index month of incident cancer diagnosis), census tract-level education level and poverty status (measured at baseline), and Medicare Part D coverage gap (measured every 120 days). Medicare Part D coverage gap or “donut hole” is the phase between the annual coverage limit and catastrophic coverage. The Part D plans typically starts with an annual deductible, after which Medicare pays for the prescription drugs up to an initial coverage limit with certain coinsurance associated with those payments. The coverage is terminated once an individual reaches the annual coverage limit until the cost of prescription drugs reaches to catastrophic limit [156].

Need-based Factors

The cancer-related factors comprised cancer diagnosis categories, stage of cancer, and cancer treatment, measured at incident cancer diagnosis. Cancer diagnosis was categorized based on cancer type and sex because the study included sex-specific cancers (breast and prostate cancer). This variable was categorized into four groups to distinguish cancer type in relation to sex, women with breast cancer, women with colorectal cancer, men with prostate cancer, and men with colorectal cancer. Stage of cancer was defined using American Joint Committee on Cancer (AJCC) classification, categorized from stage 0 to IV [181]. Cancer treatment was categorized into three groups based on cancer site, receipt of and type of initial cancer treatment (during first four months of cancer diagnosis), and cardiotoxic nature of treatment [63-67] – (a) cardiotoxic cancer treatment includes chemotherapy, hormone therapy, and/or radiotherapy for breast cancer, chemotherapy and/or hormone therapy for prostate cancer, and chemotherapy for colorectal cancer, (b) non-cardiotoxic cancer treatment includes radiation therapy for colorectal and prostate cancer and cancer surgery (all three cancers), and (c) no cancer treatment.

For CAD severity, a proxy measure was used, constructed based on the CMS hierarchical condition category (HCC) classification system. Based on the CMS risk adjustment model, each of the HCC codes for CAD was assigned specific score based on the risk and severity [154], ranging from 0.231 to 0.349, where higher scores represented severe manifestations of CAD.

Other physical and mental health conditions were selected using the Multiple Chronic Conditions working group chronic conditions grouping [155]. Physical chronic conditions, measured at baseline, were categorized into concordant (cardiac arrhythmias, congestive heart failure, diabetes, hyperlipidemia, hypertension, and stroke) and discordant (dementia, asthma, chronic obstructive pulmonary disease, arthritis, hepatitis, human immunodeficiency virus, and osteoporosis) conditions. Mental health conditions comprised severe mental illness (measured at baseline) and anxiety and depression (measured every 120 days).

Healthcare utilization

Healthcare-seeking behavior was defined as primary care and cardiologist visits, measured every 120 days.

Personal Health Care Practices

This included tobacco and alcohol use as these practices negatively impact cardiovascular health. These variables were measured every 120 days.

External Environment Factors

This domain included SEER region – Northeast (Connecticut, New Jersey), South (Kentucky, Louisiana, Atlanta, rural Georgia, and Greater Georgia), North-central (Detroit, Iowa), and West (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, Greater California), county metro status (based on urban/rural continuum codes from the AHRF), and percentage of cardiologists and oncologists in the county). These were time-invariant and measured at baseline.

3.3.6 Statistical Analyses

Unadjusted subgroup differences in time-invariant characteristics between medication adherence categories were tested with chi-square statistics. As medication adherence was measured every 120 days during pre- and post-index period, each individual had four observations. These four observations were not independent, therefore, we analyzed the relationship between adherence categories and CAD-related hospitalizations using multinomial logistic regression for repeated measures. As we are interested in describing changes in CAD-related hospitalization, given changes in adherence categories, while accounting for non-independence of observations within individuals, we selected the marginal models (i.e. population-averaged models) [182].

3.3.6.1 Inverse Probability Treatment Weight (IPTW)

As can be seen from **Table 3.1**, there were significant associations between medication adherence categories and for age, race/ethnicity, cancer type and sex, cancer stage, cancer treatment, concordant and discordant physical health conditions, mental health conditions, CAD severity, tobacco use, alcohol use, primary care visit, cardiologist visit, Part D Medicare coverage, and SEER region. Therefore, we derived IPTWs to balance the independent variables using a multinomial logistic regression on medication adherence categories during the period immediately after cancer diagnosis to take advantage of the availability of cancer-related variables (i.e. stage, cancer type, and cancer treatment). These IPTWs derived for each individual were then used as weights in CAD-related hospitalization analyses.

3.3.6.2 Instrument Variable (IV) Regression

It is plausible that there are some unobserved variables that can affect medication adherence and affect the relationship between medication adherence categories and CAD hospitalizations. IV regression is one approach to control for such unobserved selection bias. We selected the percentage of oncologists at the county-level as an

instrument variable under the assumption that the effect of oncologists on CAD-related hospitalization occurs only through medication adherence categories. For this analysis, we dichotomized adherence categories into adherent to both medication and other; CAD hospitalization was dichotomized into CAD-related hospitalization and no CAD hospitalization that included no CAD hospitalization and other hospitalizations.

Table 3.1. Multinomial Logistic Regression Models used to derive IPTW

Characteristics	No ADH 2 Rx			ADH 1 of 2 Rx			ADH 1 Rx			No ADH 1 Rx		
	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig
Age groups												
68-70 years	0.65	0.54, 0.79	***	0.99	0.85, 1.16		0.71	0.60, 0.84	***	0.75	0.63, 0.90	**
71-74 years	0.79	0.67, 0.93	**	1.01	0.88, 1.15		0.74	0.64, 0.86	***	0.70	0.59, 0.82	***
75-79 years	0.77	0.66, 0.90	**	1.01	0.89, 1.16		0.81	0.70, 0.93	**	0.72	0.61, 0.84	***
80 years and older	Ref											
Race/Ethnicity												
African Americans	1.88	1.52, 2.32	***	1.17	0.96, 1.43		1.42	1.16, 1.74	***	1.90	1.54, 2.35	***
Others	1.47	1.20, 1.80	***	1.17	0.98, 1.39		1.07	0.88, 1.30		1.12	0.90, 1.38	
Whites	Ref											
Part D Medicare coverage												
Exceeded	2.93	1.96, 4.38	***	1.51	1.14, 1.99	**	2.14	1.52, 3.01	***	3.61	2.33, 5.60	***
Not reached	1.10	0.66, 1.83		0.92	0.65, 1.32		1.09	0.71, 1.68		1.13	0.65, 1.96	
Reached												
Cancer diagnosis categories												
Women with breast cancer	0.86	0.71, 1.04		1.08	0.92, 1.25		1.54	1.31, 1.81	***	1.33	1.11, 1.60	**
Women with colorectal cancer	2.28	1.84, 2.82	***	1.71	1.42, 2.07	***	1.55	1.26, 1.92	***	2.76	2.22, 3.43	***
Men with colorectal cancer	2.31	1.88, 2.84	***	1.29	1.07, 1.56	**	1.11	0.89, 1.39		2.37	1.90, 2.95	***
Men with prostate cancer	Ref											
Cancer stage												
Stage 0/I	0.61	0.50, 0.74	***	0.89	0.75, 1.05		0.80	0.67, 0.97	*	0.67	0.55, 0.82	***
Stage II	0.76	0.64, 0.90	**	0.91	0.78, 1.07		0.87	0.74, 1.04		0.91	0.76, 1.09	
Stage III/IV	Ref											
Cancer treatment												
Cardiotoxic cancer treatment	1.00	0.83, 1.21		0.97	0.83, 1.13		0.89	0.75, 1.05		0.98	0.82, 1.19	
No cancer treatment	1.17	0.98, 1.39		0.92	0.80, 1.07		0.98	0.84, 1.14		1.01	0.84, 1.20	
Non-cardiotoxic cancer treatment	Ref			0.91	0.83, 1.00	*	0.89	0.81, 0.97	*	0.99	0.88, 1.10	
Discordant PHC												
Yes	1.29	1.14, 1.47	***	1.15	1.04, 1.28	**	1.34	1.20, 1.50	***	1.57	1.39, 1.79	***
No	Ref											
Concordant PHC												
Yes	0.66	0.49, 0.90	**	0.84	0.65, 1.10		0.49	0.38, 0.63	***	0.32	0.25, 0.41	***
No	Ref											
MHC												
Yes	1.60	1.36, 1.89	***	1.16	0.99, 1.34		1.20	1.02, 1.41	*	1.77	1.50, 2.09	***
No	Ref											
Tobacco use												
Yes	1.39	1.04, 1.85	*	1.16	0.90, 1.51		0.98	0.73, 1.31		1.12	0.83, 1.52	

Characteristics	No ADH 2 Rx			ADH 1 of 2 Rx			ADH 1 Rx			No ADH 1 Rx		
	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig	AOR	95% CI	Sig
No	Ref											
Alcohol use												
Yes	1.22	0.67, 2.20		0.99	0.58, 1.71		1.35	0.78, 2.34		2.53	1.53, 4.19	***
No	Ref											
Primary care visit												
Yes	1.34	1.11, 1.61	**	1.14	0.99, 1.32		1.00	0.87, 1.17		1.05	0.88, 1.24	
No	Ref											
Cardiologist visit												
Yes	1.03	0.90, 1.18		1.08	0.97, 1.21		0.65	0.58, 0.73	***	0.73	0.64, 0.83	***
No	Ref											
CAD severity	1.15	0.85, 1.56		0.98	0.75, 1.27		0.61	0.46, 0.83	**	0.69	0.50, 0.96	*
SEER Region												
Northeast	1.04	0.88, 1.22		1.07	0.94, 1.22		1.15	1.00, 1.33	*	0.92	0.78, 1.08	
South	1.24	1.06, 1.46	**	1.17	1.02, 1.33	*	1.05	0.91, 1.22		1.10	0.94, 1.29	
North-central	0.92	0.76, 1.11		1.01	0.87, 1.18		0.96	0.82, 1.14		0.76	0.62, 0.92	**
West	Ref											

Based on 12,096 elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, and prostate cancer. Weights were derived using the Inverse Probability Treatment Weighting approach.

Description of medication use and adherence

No ADH 2 Rx: Not adherent to both statins and ACEIs/ARBs/beta-blockers;

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers;

ADH 1 Rx: Use of one medication class and adherent to that class;

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in study population characteristics (time-invariant). Reference category is *Adherent to both statins and ACEIs/ARBs/beta-blockers*

***p < 0.001; **0.001 ≤ p < 0.01; *0.01 ≤ p < 0.05.

Time-invariant characteristics include cancer diagnosis categories, age, race/ethnicity, concordant and discordant physical health conditions, CAD severity, SMI, SEER region. Time-variant characteristics include tobacco use, alcohol use, depression, anxiety, and routine follow-up with primary care physician and/or cardiologist, and Part D Medicare coverage.

Concordant physical health conditions consisted of diabetes, hyperlipidemia, hypertension, stroke, cardiac arrhythmia, and congestive heart failure. Discordant physical health conditions consisted of arthritis, asthma, chronic obstructive pulmonary disease, osteoporosis, dementia, human immunodeficiency virus, and hepatitis. Mental health conditions include anxiety, depression, SMI (schizophrenia, bipolar disorder, and psychoses)

Abbreviations

ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; CAD: Coronary artery disease; FFS: Fee-for-service; IPTW: inverse probability treatment weighting; MHC: Mental health conditions; PHC: Physical health conditions; Ref: Reference; Rx: Prescription; SEER: Surveillance, Epidemiology and End Results

3.4 Results

3.4.1 Characteristics of the Study Population

The study population comprised 12,096 elderly FFS Medicare beneficiaries with pre-existing CAD and incident cancer diagnosis. There were 33.1% women with breast cancer, 14.1% women with colorectal cancer; 11.6% men with colorectal cancer, and 41.2% men with prostate cancer (**Table 3.2**). Nearly one-third (29.5%) were diagnosed with stage 0 or I. Only 16.8% received no cancer treatment.

3.4.1.1 Characteristics of the Study Population by Medication Adherence Categories - Before and After IPTW Adjustment

Table 3.3 summarizes the characteristics of the cohort by adherence to statins and/or ACEIs/ARBs/beta-blockers before and after IPTW adjustment. Prior to IPTW adjustment, there were statistically significant differences in age, race/ethnicity, cancer type and sex, cancer stage, cancer treatment, concordant physical conditions, discordant physical conditions, mental health conditions, tobacco use, alcohol use, any primary care visit, cardiologist visit, Part D Medicare coverage, and SEER region between the medication adherence groups. After IPTW adjustment, there were no significant differences in these variables between the medication adherence groups.

Adherence to both statins and ACEIs/ARBs/beta-blockers was estimated at 31.2% during the 120-day period immediately after cancer diagnosis; 13.7% were not adherent to both medication classes during the same period. **Table 3.4** summarizes the CAD-related hospitalizations over time. The prevalence of CAD-related hospitalizations was 27.4% during the 120-day period immediately after cancer diagnosis and this percentage declined to 10.6% during the last four months of post-cancer period.

Table 3.2. Selected Characteristics of Study Population

Characteristics	Total population	
	N	%
Age groups		
68-70 years	1,983	16.4
71-74 years	2,887	23.9
75-79 years	3,158	26.1
80 years and older	4,068	33.6
Race/Ethnicity		
Whites	9,928	82.1
African Americans	1,013	8.4
Others	1,155	9.5
Cancer diagnosis		
Women with breast cancer	4,007	33.1
Women with colorectal cancer	1,705	14.1
Men with colorectal cancer	1,399	11.6
Men with prostate cancer	4,985	41.2
Cancer stage		
Stage 0/I	3,565	29.5
Stage II	6,572	54.3
Stage III/IV	1,959	16.2
Cancer treatment		
Cardiotoxic cancer treatment	4,821	34.9
Non-cardiotoxic cancer treatment	6,668	48.3
No cancer treatment	2,322	16.8
SEER Region		
Northeast	2,749	22.7
South	2,977	24.6
North-central	1,691	14.0
West	4,679	38.7
Index year		
2008	2,966	24.5
2009	2,975	24.6
2010	2,992	24.7
2011	3,163	26.1

Note: Based on 12,096 elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, and prostate cancer between 2008 and 2011. Table includes time-invariant characteristics.

Abbreviation: SEER: Surveillance, Epidemiology and End Results

Table 3.3. Unweighted and Weighted Percent of Selected Characteristics by Adherence to Statins and/or ACEIs/ARBs/Beta-blockers

Characteristics	Before IPTW (%)						After IPTW (Wt. %)					
	ADH 2 Rx	No ADH 2 Rx	ADH 1 of 2 Rx	ADH 1 Rx	No ADH 1 Rx	Sig	ADH 2 Rx	No ADH 2 Rx	ADH 1 of 2 Rx	ADH 1 Rx	No ADH 1 Rx	Sig
Age groups						***						NS
68-70 years	18.0	13.7	17.1	14.9	16.3		16.5	16.8	16.3	16.5	16.6	
71-74 years	25.7	23.3	24.9	22.0	21.1		24.0	23.8	23.9	24.0	24.0	
75-79 years	27.3	24.6	27.2	25.9	23.4		26.4	26.0	25.9	25.8	26.3	
80 years and older	29.0	38.4	30.8	37.2	39.2		33.1	33.4	33.8	33.8	33.0	
Race/Ethnicity						***						NS
Whites	84.5	77.6	82.7	82.4	79.6		82.2	81.6	82.2	81.7	82.3	
African Americans	6.4	10.8	7.6	8.8	11.2		8.4	8.4	8.2	8.5	8.5	
Others	9.1	11.6	9.8	8.8	9.3		9.4	10.0	9.5	9.7	9.2	
Part D Medicare coverage						***						NS
Exceeded	5.6	2.7	3.9	3.4	2.4		4.1	4.3	4.0	4.1	3.8	
Not reached	90.5	95.4	93.1	94.5	96.1		93.2	93.1	93.3	93.1	93.4	
Reached	3.8	1.9	3.0	2.1	1.5		2.8	2.6	2.7	2.8	2.7	
Cancer diagnosis categories						***						NS
Women with breast cancer	33.8	23.3	32.5	41.6	31.2		34.0	33.5	33.2	33.5	33.5	
Women with colorectal cancer	9.3	21.2	14.8	12.1	19.4		13.7	13.9	14.1	13.8	13.7	
Men with colorectal cancer	9.5	19.0	11.0	7.9	14.6		11.3	11.4	11.4	11.7	11.4	
Men with prostate cancer	47.4	36.5	41.7	38.4	34.8		41.0	41.3	41.3	41.0	41.3	
Cancer stage						***						NS
Stage 0/I	29.2	25.9	30.3	32.6	27.9		29.8	29.4	29.4	29.4	29.8	
Stage II	57.4	51.9	53.8	52.5	53.0		54.0	55.0	54.4	54.3	54.1	
Stage III/IV	13.4	22.1	15.8	14.9	19.1		16.2	15.6	16.2	16.3	16.1	
Cancer treatment						***						NS
Cardiotoxic cancer treatment	37.3	30.3	36.5	35.4	33.2		35.7	36.1	35.4	35.3	35.5	
Non-cardiotoxic cancer treatment	16.8	14.7	16.7	16.7	16.0		16.5	16.8	16.3	16.5	16.2	
No cancer treatment	45.9	55.0	46.8	47.8	50.9		47.9	47.1	48.3	48.2	48.3	
Discordant PHC						***						NS
Yes	35.7	43.4	39.6	43.2	47.1		40.7	41.0	40.9	40.9	40.8	
No	64.3	56.6	60.4	56.8	52.9		59.3	59.0	59.1	59.1	59.2	
Concordant PHC						***						NS
Yes	96.6	95.8	96.3	93.8	91.5		95.2	95.4	95.2	95.3	95.1	
No	3.4	4.2	3.7	6.2	8.5		4.8	4.6	4.8	4.7	4.9	
MHC						*						NS
Yes	11.9	18.8	14.1	14.6	20.5		15.0	14.3	14.9	15.0	14.8	
No	88.1	81.2	85.9	85.4	79.5		85.0	85.7	85.1	85.0	85.2	

Characteristics	Before IPTW (%)						After IPTW (Wt. %)					
	ADH 2 Rx	No ADH 2 Rx	ADH 1 of 2 Rx	ADH 1 Rx	No ADH 1 Rx	Sig	ADH 2 Rx	No ADH 2 Rx	ADH 1 of 2 Rx	ADH 1 Rx	No ADH 1 Rx	Sig
Tobacco use						**						NS
Yes	3.4	5.3	4.3	3.5	4.7		3.9	4.4	4.0	4.0	3.7	
No	96.6	94.7	95.7	96.5	95.3		96.1	95.6	96.0	96.0	96.3	
Alcohol use						***						NS
Yes	0.8	1.1	0.9	1.0	2.2		0.9	1.0	1.1	1.0	0.9	
No	99.2	98.9	99.1	99.0	97.8		99.1	99.0	98.9	99.0	99.1	
Primary care visit						***						NS
Yes	83.0	89.4	85.9	84.7	86.8		85.2	84.7	85.3	85.4	85.3	
No	17.0	10.6	14.1	15.3	13.2		14.8	15.3	14.7	14.6	14.7	
Cardiologist visit						***						NS
Yes	68.1	73.2	71.1	59.6	64.5		66.8	67.6	67.2	67.4	66.7	
No	31.9	26.8	28.9	40.4	35.5		33.2	32.4	32.8	32.6	33.3	
SEER Region						*						NS
Northeast	22.9	21.4	22.8	24.6	20.5		22.5	21.9	22.7	22.4	22.7	
South	23.4	25.8	25.5	23.4	26.6		25.0	25.6	24.7	24.9	24.7	
North-central	14.8	13.1	13.8	14.4	12.3		13.9	13.6	13.9	13.8	14.3	
West	38.8	39.7	37.9	37.6	40.5		38.6	38.9	38.7	39.0	38.4	

Note: Based on 12,096 elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, and prostate cancer diagnosis.

Weights were derived using the Inverse Probability Treatment Weighting approach.

Description of medication use and adherence

ADH 2 Rx: Adherent to both statins and ACEIs/ARBs/beta-blockers;

No ADH 2 Rx: Not adherent to both statins and ACEIs/ARBs/beta-blockers;

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers;

ADH 1 Rx: Use of one medication class and adherent to that class;

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in time-invariant patient-level characteristics based on chi-square tests

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$. Column percentages are reported.

Time-invariant characteristics include cancer diagnosis categories, age, race/ethnicity, concordant and discordant physical health conditions, SMI, SEER region. Time-variant characteristics include tobacco use, alcohol use, depression, anxiety, and routine follow-up with primary care physician and/or cardiologist, and Part D Medicare coverage.

Concordant physical health conditions consisted of diabetes, hyperlipidemia, hypertension, stroke, cardiac arrhythmia, and congestive heart failure. Discordant physical health conditions consisted of arthritis, asthma, chronic obstructive pulmonary disease, osteoporosis, dementia, human immunodeficiency virus, and hepatitis. Mental health conditions include anxiety, depression, SMI (schizophrenia, bipolar disorder, and psychoses)

Abbreviations

ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; CAD: Coronary artery disease; FFS: Fee-for-service; IPTW: inverse probability treatment weighting; MHC: Mental health conditions; PHC: Physical health conditions; Rx: Prescription; SEER: Surveillance, Epidemiology and End Results; Wt.: Weighted

Table 3.4. Weighted percentage with CAD-related hospitalizations over different time periods

Use and adherence to CAD-related pharmacotherapy	Pre-cancer dx period	Initial cancer tx period	Post-tx period	
	t ₀	t ₁	t ₂	t ₃
	Wt. %	Wt. %	Wt. %	Wt. %
CAD-related hospitalization				
ADH 2 Rx	7.5	28.6	8.9	7.6
No ADH 2 Rx	10.4	31.4	18.0	14.7
ADH 1 of 2 Rx	8.5	28.1	12.6	11.2
ADH 1 Rx	5.7	19.9	7.3	7.1
No ADH 1 Rx	7.6	22.7	9.7	10.2
Other hospitalization				
ADH 2 Rx	2.1	14.2	3.5	2.6
No ADH 2 Rx	3.6	18.3	7.0	6.2
ADH 1 of 2 Rx	2.8	17.4	3.9	4.4
ADH 1 Rx	3.2	22.7	5.7	4.0
No ADH 1 Rx	4.3	23.8	8.0	6.3

Note: Based on 12,096 elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, and prostate cancer diagnosis. Weights were derived using the Inverse Probability Treatment Weighting approach.

Description of medication use and adherence

ADH 2 Rx: Adherent to both statins and ACEIs/ARBs/beta-blockers;

No ADH 2 Rx: Not adherent to both statins and ACEIs/ARBs/beta-blockers;

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers;

ADH 1 Rx: Use of one medication class and adherent to that class;

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Abbreviations

CAD: Coronary artery disease

3.4.1.2 Unadjusted and Adjusted Associations between Adherence to Statins and/or ACEIs/ARBs/Beta-blockers and CAD-related Hospitalization

Table 3.5 displays the results from the unadjusted and adjusted multinomial logistic regression models with IPTW for repeated measures on CAD-related hospitalization. The adjusted model controlled for time, age, race/ethnicity, census tract education level and poverty status, marital status, Part D Medicare coverage, concordant and discordant physical health conditions, and mental health conditions, cancer type and sex, cancer stage, cancer treatment, tobacco use, alcohol use, visits to primary care/cardiologist, SEER region, and county metro status. Reference category for the dependent variable was *no CAD hospitalization*.

In unadjusted analyses, those not adherent to both medication classes [OR = 1.67; 95% CI = 1.58, 1.76; $P < 0.0001$] and those who were adherent to one (out of two) medication class [OR = 1.22; 95% CI = 1.15, 1.30; $P < 0.0001$] were more likely to have CAD-related hospitalization, compared to those who were adherent to both medication classes. However, those with the use of one medication class and adherent to that medication class were significantly less likely to have CAD-related hospitalization compared to those who were adherent to both medication classes [OR = 0.76; 95% CI = 0.66, 0.86; $P < 0.0001$].

Consistent with the findings from unadjusted model, compared to those who were adherent to both medication classes, those not adherent to both medication classes [AOR = 1.82; 95% CI = 1.72, 1.92; $P < 0.0001$] and those who were adherent to one (out of two) medication class [AOR = 1.26; 95% CI = 1.17, 1.34; $P < 0.0001$] were more likely to have CAD-related hospitalization in the adjusted model. Further, those with the use of one medication class and adherent to that medication class were significantly less likely to have CAD-related hospitalization compared to those who were adherent to both medication classes [AOR = 0.80; 95% CI = 0.70, 0.90; $P < 0.0001$]. However, those with use of one medication class and not adherent to that medication class [AOR = 1.20; 95% CI = 1.09, 1.31; $P = 0.005$] were more likely to have CAD-related hospitalization.

Table 3.5. Odds Ratios, Adjusted Odds Ratios, and 95% Confidence Intervals of Medication Adherence Categories from Multinomial Logistic Regression Models with Repeated Measures on Hospitalization Categories – IPTW (Reference Group = No Hospitalizations)

Variables	CAD-related hospitalization			Other hospitalization		
	OR	95% CI	Sig	OR	95% CI	Sig
Unadjusted analysis						
Medication adherence categories						
No ADH 2 Rx	1.67	[1.58,1.76]	***	1.88	[1.75,2.00]	***
ADH 1 of 2 Rx	1.22	[1.15,1.30]	***	1.36	[1.25,1.46]	***
ADH 1 Rx	0.76	[0.66,0.86]	***	1.59	[1.48,1.70]	***
No ADH 1 Rx	1.05	[0.94,1.15]		2.10	[1.99,2.22]	***
ADH 2 Rx		Reference			Reference	
Cancer diagnosis categories						
Women with breast cancer	1.15	[1.07,1.23]	***	1.61	[1.52,1.70]	***
Women with colorectal cancer	3.39	[3.31,3.47]	***	4.23	[4.14,4.32]	***
Men with colorectal cancer	3.60	[3.52,3.68]	***	2.91	[2.80,3.02]	***
Men with prostate cancer		Reference			Reference	
Cancer stage						
Stage 0/I	0.93	[0.87,0.99]	*	0.82	[0.77,0.88]	***
Stage III/IV	2.04	[1.97,2.12]	***	2.31	[2.22,2.40]	***
Stage II		Reference			Reference	
Cancer treatment						
Cardiotoxic cancer treatment	1.30	[1.16,1.44]	***	2.36	[2.16,2.56]	***
No cancer treatment	0.88	[0.76,1.00]	*	1.11	[0.93,1.29]	
Non-cardiotoxic cancer treatment		Reference			Reference	
Adjusted analysis						
Variables	AOR	95% CI	Sig	AOR	95% CI	Sig
Medication adherence categories						
No ADH 2 Rx	1.82	[1.72,1.92]	***	2.00	[1.87,2.13]	***
ADH 1 of 2 Rx	1.26	[1.17,1.34]	***	1.39	[1.28,1.49]	***
ADH 1 Rx	0.80	[0.70,0.90]	***	1.65	[1.54,1.76]	***
No ADH 1 Rx	1.20	[1.09,1.31]	**	2.34	[2.22,2.46]	***
ADH 2 Rx		Reference			Reference	
Cancer diagnosis categories						
Women with breast cancer	1.18	[1.08,1.29]	**	1.59	[1.47,1.71]	***
Women with colorectal cancer	3.31	[3.20,3.42]	***	4.20	[4.07,4.33]	***
Men with colorectal cancer	3.78	[3.67,3.88]	***	2.80	[2.67,2.93]	***
Men with prostate cancer		Reference			Reference	
Cancer stage						
Stage 0/I	0.65	[0.55,0.74]	***	0.71	[0.60,0.81]	***
Stage III/IV	1.25	[1.15,1.34]	***	1.37	[1.26,1.47]	***
Stage II		Reference			Reference	
Cancer treatment						
Cardiotoxic cancer treatment	1.31	[1.14,1.49]	**	2.14	[1.91,2.37]	***
No cancer treatment	0.84	[0.69,0.98]	*	1.07	[0.86,1.28]	
Non-cardiotoxic cancer treatment		Reference			Reference	

Note: Based on 12,096 elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, and prostate cancer diagnosis. Weights were derived using the Inverse Probability Treatment Weighting approach.

Description of medication use and adherence

ADH 2 Rx: Adherent to both statins and ACEIs/ARBs/beta-blockers;

No ADH 2 Rx: Not adherent to both statins and ACEIs/ARBs/beta-blockers;

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers;

ADH 1 Rx: Use of one medication class and adherent to that class;

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in medication adherence groups, derived from multinomial logistic regression models with repeated measures. Reference category for dependent variable is ***no hospitalization***.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

ORs are reported for unadjusted GEE model and AORs are reported for adjusted GEE model.

Adjusted model controlled for independent variables. Time-invariant characteristics include cancer diagnosis categories, age, race/ethnicity, poverty status, high school education, concordant and discordant physical health conditions, SMI, SEER region, and county-level characteristics. Time-variant characteristics include, tobacco use, alcohol use, depression, anxiety, and routine follow-up with primary care physician and/or cardiologist, and Part D Medicare coverage.

Abbreviations

AOR: Adjusted odds ratio; CAD: Coronary artery disease; CI: Confidence interval; FFS: Fee-for-service; GEE: Generalized estimating equations; OR: Odds ratio; IPTW: Inverse Probability treatment weighting; Sig: Significance; SEER: Surveillance, Epidemiology, and End Result.

3.4.2 Sensitivity Analyses

We found that the percent of oncologists at the county-level was a strong and valid instrument variable. The variable oncologists at the county-level were significantly associated with medication adherence [OR = 4.27; 95% CI = 2.15, 8.47; $P < 0.0001$] and medication adherence was an endogenous variable [Wald test, $P < 0.0001$]. Results from IV regression revealed that Medicare beneficiaries in other medication adherence category (not adherent to one or both medication classes) were more likely to have CAD-related hospitalization compared to those who were adherent to both medication classes [Beta = 1.20; SE = 0.10; $P < 0.0001$]. The results did not change when medication adherence was categorized into three categories, those not adherent to one or both medication classes were more likely to have CAD-related hospitalization [Beta = 1.22; SE = 0.12; $P < 0.0001$], whereas those with single medication use and adherent to that medication [Beta = -0.98; SE = 0.13; $P < 0.0001$] were less likely to have CAD-related hospitalization when compared to those adherent to both medications.

Table 3.6 displays the AORs and 95% CI for from the adjusted multinomial logistic regressions on CAD-related hospitalization that accounted for IPTW and repeated measures, where CAD-related hospitalizations were identified from primary diagnosis. There were some similarities and differences in comparison to GEE model with hospitalization identified from both primary and secondary diagnosis (*primary analyses*).

Consistent with the *primary analyses* (adjusted model), those who were not adherent to both medication classes [AOR = 2.57; 95% CI = 2.41, 2.74; $P < 0.0001$], adherent to one (out of two) medication class [AOR = 1.42; 95% CI = 1.27, 1.57; $P < 0.0001$], or were using single medication class and not adherent to that medication class [AOR = 1.42; 95% CI = 1.27, 1.57; $P = 0.0002$] were more likely to have CAD-related hospitalization compared to those who were adherent to both medication classes. However, in contrast to the *primary analyses*, there was no significant difference in those using one medication class and adherent to that medication class compared to those who were adherent to both medication classes.

3.4.3 Adjusted Associations between Other Independent Variables and CAD Hospitalization

Appendix 4 displays the AORs and 95% CI from the adjusted GEE models with IPTW on adherence for other independent variables. Other variables, such as cancer diagnosis categories, cancer stage, and cancer treatment were significantly associated with CAD-related hospitalization categories. Compared to men with prostate cancer, women with breast cancer [AOR = 1.18; 95% CI = 1.08, 1.29], women with colorectal cancer [AOR = 3.31; 95% CI = 3.20, 3.42], and men with colorectal cancer [AOR = 3.78; 95% CI = 3.67, 3.88] were more likely to have CAD-related hospitalizations. Those with cancer stage III/IV *versus* stage II [AOR = 1.25; 95% CI = 1.15, 1.34] and those receiving cardiotoxic cancer treatment *versus* no cardiotoxic cancer treatment [AOR = 1.31; 95% CI = 1.14, 1.49] were more likely to have CAD-related hospitalization.

Table 3.6. Sensitivity analysis: CAD Hospitalization Identified from Primary Diagnosis Odds Ratios, Adjusted Odds Ratios, and 95% Confidence Intervals of Medication Adherence Categories GEE Models with IPTW on CAD Hospitalization

Medication adherence categories	CAD-related hospitalization			Other hospitalization		
	OR/AOR	95% CI	Sig	OR/AOR	95% CI	Sig
Unadjusted GEE analysis						
No ADH 2 Rx	2.36	[2.20,2.52]	***	1.61	[1.53,1.70]	***
ADH 1 of 2 Rx	1.38	[1.24,1.52]	***	1.24	[1.17,1.31]	***
ADH 1 Rx	0.76	[0.56,0.95]	**	1.06	[0.98,1.13]	
No ADH 1 Rx	1.23	[1.03,1.43]	*	1.39	[1.31,1.47]	***
ADH 2 Rx	Reference			Reference		
Adjusted GEE analysis						
No ADH 2 Rx	2.57	[2.41,2.74]	***	1.75	[1.66,1.84]	***
ADH 1 of 2 Rx	1.42	[1.27,1.57]	***	1.27	[1.20,1.35]	***
ADH 1 Rx	0.83	[0.63,1.02]		1.11	[1.03,1.19]	**
No ADH 1 Rx	1.46	[1.26,1.66]	***	1.58	[1.49,1.67]	***
ADH 2 Rx	Reference			Reference		

Note: Based on 12,096 elderly fee-for-service Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, and prostate cancer diagnosis. Weights were derived using the Inverse Probability Treatment Weighting approach.

Description of medication use and adherence

ADH 2 Rx: Adherent to both statins and ACEIs/ARBs/beta-blockers;

No ADH 2 Rx: Not adherent to both statins and ACEIs/ARBs/beta-blockers;

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers;

ADH 1 Rx: Use of one medication class and adherent to that class;

No ADH 1 Rx: Use of one medication class and not adherent to that medication class

Asterisks represent significant differences in medication adherence groups, derived from GEE. Reference category for dependent variable is *no hospitalization*.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

ORs are reported for unadjusted GEE model and AORs are reported for adjusted GEE model.

Adjusted model controlled for independent variables. Time-invariant characteristics include cancer diagnosis categories, age, race/ethnicity, poverty status, high school education, concordant and discordant physical health conditions, SMI, SEER region, and county-level characteristics. Time-variant characteristics include, tobacco use, alcohol use, depression, anxiety, and routine follow-up with primary care physician and/or cardiologist, and donut hole.

Abbreviations

AOR: Adjusted odds ratio; CAD: Coronary artery disease; CI: Confidence interval; FFS: Fee-for-service; GEE: Generalized estimating equations; OR: Odds ratio; IPTW: Inverse Probability treatment weighting; Sig: Significance; SEER: Surveillance, Epidemiology, and End Results

3.5 Discussion

To the best of our knowledge, this is the first study to examine the impact of adherence to statins and ACEIs/ARBs/beta-blockers on CAD hospitalizations in elderly FFS Medicare beneficiaries with pre-existing CAD and incident cancer diagnosis. Compared to Medicare beneficiaries with CAD and cancer who were adherent to both statins and ACEIs/ARBs/beta-blockers, those who were non-adherent to either both or single medication classes were more likely to have CAD-related hospitalization. Findings from the current study are consistent with published literature that is not specific to cancer. In these studies, non-adherence to statins and ACEIs/ARBs/beta-blockers has been reported to have negative cardiovascular health consequences, including cardiovascular events and hospitalization [94-96].

Counterintuitively, our study findings indicated that those using single medication class and adherent to that single medication class were less likely to have CAD-related hospitalization compared to those who were adherent to both medication classes. This is an unanticipated finding and plausible reasons could be that this specific population may have lower CAD severity or may be different in unobserved characteristics such as healthy eating, exercise, and maintaining normal weight. Further research is needed to understand the role of these factors in reducing CAD-related hospitalizations in the elderly Medicare beneficiaries with CAD. Interestingly, in a sensitivity analysis where CAD hospitalization was the primary diagnosis, no significant difference was observed between single medication users (adherent) and those adherent to both medication classes.

Consistent with a previous study on patients with prostate cancer diagnosis [170], we observed that CAD-related hospitalizations increased in the period immediately after cancer diagnosis for all medication adherence categories. As stated in the introduction, cardiotoxic cancer treatments can increase the risk of CAD-related hospitalizations [60-62]. This is also evident from our study findings, where those receiving cardiotoxic cancer treatment were more likely to have CAD-related hospitalizations compared to those not receiving non-cardiotoxic cancer treatment.

A meta-analysis of clinical trials showed that the prophylactic use of beta-blockers, ACEI, ARBs, or statins reduced the risk of newly developed heart failure in patients administered anthracycline [71]. We assessed the interaction between medication adherence categories and cancer treatment on CAD-related hospitalization. Our study findings revealed that the interaction effect between adherence to both medication classes and cardio-toxic cancer treatment was not statistically significant. It is possible that the established CAD diminishes the cardio-protective effect of these medications. In addition, the meta-analysis did not specifically focus on elderly population and specific cancers included in our study. Future studies that include characteristics that were not measured in the current study (example: physical activity, alternative and complementary medicine, polypharmacy) are needed to provide conclusive evidence on the lack of interaction between adherence and cardio-toxic cancer treatment.

3.5.1 Clinical and Policy Implications

Both CAD and cancer are life-threatening conditions and co-management of both conditions can be challenging. However, lack of effective management of CAD may not only increase CAD complications, but can also have negative consequences for cancer prognosis. Current clinical practices recommend stabilizing pre-existing

CAD prior to initiating cancer treatment. For example, appropriate pharmacologic management (statins and beta-blockers) of the patient with pre-existing CAD is recommended for those undergoing cancer surgery [72]. Given the complexity of interaction between CAD and cancer, it is important to routinely monitor medication adherence in general clinical practice and provide linkages to support services that can increase medication adherence. This may warrant integration of cardiovascular care in the elderly diagnosed with incident cancer. An example of integrated care is the cardio-oncology clinics that provide interdisciplinary and integrative management approach to cancer patients with cardiovascular risks or conditions [183].

It is possible that certain CAD-related hospitalizations in our study may be readmission or preventable hospitalizations, which have policy implications. The Affordable Care Act, under Hospital Readmissions Reduction Program, provided CMS the authority to reduce payments to certain hospital readmissions that it deemed avoidable [184]. The emphasis was on Medicare readmissions related to heart failure, myocardial infarction, and pneumonia. Reducing avoidable readmissions can enhance patient quality of care and lower health care spending. In addition, based on Agency for Healthcare Research and Quality's (AHRQ) prevention quality indicators, hospitalizations related to conditions, such as angina without procedure and congestive heart failure, are considered preventable hospitalizations with good outpatient care. Therefore, it is important to implement interventions for improving medication adherence and to have integrated care for patients with pre-existing CAD and incident cancer diagnosis for reducing avoidable hospitalizations.

3.5.2 Strengths and Limitations

Our study findings need to be interpreted in the context of its limitations. First, the study findings cannot be generalized to all Medicare beneficiaries because the study population is restricted to those residing in SEER regions and to those with FFS Medicare plans. Further, the study population was restricted to elderly population with breast, colorectal, or prostate cancer and pre-existing CAD. The findings cannot be generalized to younger population or those with other cancer types. Second, we were not able to control for many other variables such as lifestyle health behaviors, knowledge, attitude, preferences and other factors that may affect adherence as well as hospitalizations [185]. Further, we did not look at specific cardiotoxic agents, which to some extent have overestimated cardiotoxicity measure in the study. However, we controlled for a comprehensive list of variables to examine multivariable associations. We used a proxy measure for CAD severity, which may not reflect the precise CAD severity in the population. Gold standards for measuring CAD severity, such as stress tests, are not available in Medicare database. Lastly, we used prescription claims for measuring adherence. As part D file contains only filled prescriptions, it is not known whether the patient actually used the medications or whether the patients adhered to their providers' instructions or not.

Despite these limitations, our study adds to the nascent literature on cardio-oncology and has several strengths. First, the current study included a large cohort of patients over a long period of time across a variety of providers and focused on real-world practice patterns. Second, the study used a robust repeated measure design. Third, the study used a variety of statistical methods to control for both observed and unobserved selection bias to ensure robustness of findings.

3.5.3 Conclusions

Non-adherence to both statins, ACEIs/ARBs/beta blockers can increase the risk other CAD-related hospitalizations in pre-existing CAD and incident breast, colorectal, or prostate cancer. Future studies need to examine the role of patient-related factors that were not measured in this study on adherence so that strategies to improve adherence in this population can be developed.

CHAPTER 4

Impact of Incident Cancer on Short-term CAD-related Medicare Expenditures among Medicare Beneficiaries with Pre-existing Coronary Artery Disease

4.1 Abstract

Objectives: To examine the association between incident cancer and short-term coronary artery disease (CAD)-related Medicare expenditures among elderly with incident breast, colorectal and prostate cancer.

Methods: A retrospective observational longitudinal study was conducted among elderly Medicare fee-for-service beneficiaries with pre-existing CAD and those with incident breast (BC), colorectal (CC), or prostate (PC) cancer (N = 12,095) and those with no cancer (NC) (N = 34,237). CAD-related healthcare expenditures were measured every 120 days during the one-year pre- and one-year post-index period. Due to the overlap between cancer type and sex, cancer diagnosis was grouped into: (1) women with BC; (2) women with CC; (3) women with NC; (4) men with PC; (5) men with CC; and (6) men with NC. CAD-related healthcare expenditures consisted of the actual Medicare payments for inpatient, home healthcare (HHA), and outpatient services corresponding to the ICD-9-CM primary and secondary diagnosis code for CAD. The adjusted relationship between incident cancer and CAD-related expenditures was analyzed using the generalized linear mixed models (GLMM). Inverse probability treatment weights were used to account for observed group differences between cancer and non-cancer groups.

Results: Overall, CAD-related mean healthcare expenditures at pre-index period accounted for about 32.6% - 39.5% of total expenditures among women and 41.5% - 46.8% among men. In the adjusted GLMM, all cancer groups had significantly higher CAD-related healthcare expenditures compared to the non-cancer groups. Women with CC 153% higher expenditures compared to women with no cancer [$\beta = 0.93$, $P < 0.0001$]. Men with CC had 166% higher expenditures compared to men with NC [$\beta = 0.98$, $P < 0.0001$]. Further, men and women with CC had 57% and 55% higher expenditures compared to men with PC and women with BC, respectively.

Conclusions: CAD-related Medicare expenditures were higher for those with cancer as compared to Medicare beneficiaries without cancer. Elderly with CC were particularly vulnerable for high CAD-related expenditures. These study findings make a compelling case for of designing effective programs and policies to reduce CAD-related expenditures. Close monitoring and surveillance of CC patients with CAD may be needed to prevent CAD-related events and expenditures.

4.2 Introduction

In 2013, cardiovascular disease, which included coronary artery disease (CAD) and cerebrovascular disease, ranked first in healthcare expenditures with an estimated \$231.1 billion among a mutually exclusive list of 155 conditions [186]. It has also been documented that healthcare spending for services directly resulting from CAD (i.e. CAD-related expenditures such as) were higher than for other chronic conditions [187, 188]. For these individuals, CAD-related expenditures can be higher than those with only CAD [189]. Furthermore, CAD-related healthcare expenditures in the United States (US) are projected to increase by 198% in 2030 with increase in aging population [187].

Evidence also suggests that individuals with CAD have many pre-existing conditions or due to the shared risk factor, may develop new conditions such as cancer [190]. For these individuals, CAD-related expenditures can be higher than those with only CAD [56, 189]. Specifically, CAD-related expenditures may be higher among individuals with incident cancer (and CAD) during the period immediately after cancer diagnosis because of several reasons: 1) cardiotoxicity from specific cancer treatments can exacerbate pre-existing CAD [60, 61, 72]; and 2) diagnosis of incident cancer may impede with the management of CAD, thereby increasing the risk of CAD-related complications, given that cancer is considered a dominant condition [69].

However, there is a dearth of studies on the impact of cancer on CAD-related expenditures. It is important to analyze CAD-related expenditures among Medicare beneficiaries because there are large differences in healthcare expenditures directly attributed to CAD and total expenditures of a person with CAD [187]. More specifically, published studies suggest that inpatient accounts for nearly 43% of total expenditures for cardiovascular diseases [191]. Furthermore, CAD-related expenditures may be higher among elderly due to aging. For example, Dieleman et al. reported that 65.2% of expenditures for CAD and related diseases were for individuals 65 years and older, suggesting that elderly individuals account for most of the expenditures for CAD care [186]. As nearly 84% of the elderly are covered by Medicare [99], payments made by Medicare for CAD are substantial, suggesting that it is important to estimate Medicare payments for CAD care. In 2012, the Medicare program paid \$273 billion for heart disease, with per-person cost of \$10,345 [192].

Estimating the extent to which incident cancer affects CAD-related expenditures can help the payers with the emerging healthcare delivery reform initiatives, which are focused on financial incentives to improve healthcare quality with lower healthcare expenditures. For example, new payment models from the Centers for Medicare and Medicaid Services (CMS) support bundled payments for episodes of care. One of the experimental initiatives will support bundled payments for clinicians providing care to patients with CAD [193]. Such models have the potential to be extended to those who develop cancer after CAD. In addition, estimating payments for CAD-related care may also help providers by reducing costs and increasing coordination across providers. For example, Medicare Access and Children's Health Insurance Program Reauthorization Act (MACRA) of 2015, a payment reform by Medicare has created alternative payment models [193], provides financial incentives for providing value-based care and penalties for poor quality of care. These models require risk adjustment of patients [194-196], and therefore, identifying who are at risk for high-cost is important.

The present study examined the impact of cancer on CAD-related expenditures using data from a cohort of elderly fee-for-service (FFS) Medicare beneficiaries with and without cancer. We also analyzed CAD-related inpatient expenditures and outpatient expenditures. The cancer cohort consisted of elderly with incident breast, colorectal or prostate cancer. These cancers were selected as they have a higher prevalence among elderly population with [107] and pre-existing CAD is highly prevalent among the elderly diagnosed with these cancers [109-112, 114, 197].

4.3 Methods

4.3.1 Conceptual Framework

The conceptual framework was adapted based on the Andersen's Behavioral Model of Health Service Use for understanding CAD-related healthcare expenditures and a priori selection of independent variables (**Figure 1.3**) [124, 125]. This model posits that individual's predisposing (age, sex, race/ethnicity), enabling (marital status, prescription drug coverage, census tract, and poverty status), need factors (chronic physical and mental health conditions), personal health practices (tobacco and alcohol use), healthcare use (visits to primary care/cardiologist and adherence to CAD medications) and external environment (Surveillance, Epidemiology and End Results [SEER] region and county metro status) may influence healthcare expenditures [126].

4.3.2 Study Design

A retrospective observational longitudinal cohort design with a 12-month pre- and 12-month post-index period was used (**Figure 2.1**). For the cancer cohort, pre- and post-index periods were based on cancer diagnosis dates. For the non-cancer cohort, pre- and post-index periods were derived using pseudo-diagnosis dates, which were randomly selected from the dates of service. Each individual was observed for 48 months with 24-month baseline (for identification of CAD and baseline characteristics) period, 12-month pre-index, and 12-month post-index periods. CAD-related healthcare expenditures and selected independent variables were measured repeatedly every 120 days during the pre- (t_1 , t_2 , and t_3) and post-index (t_4 , t_5 , and t_6) period, yielding a total of six repeated measures for every single individual.

4.3.3 Data Sources

The data were linked from different sources, including the SEER registries; Medicare claims linked with the SEER registries; 5% non-cancer random sample of Medicare beneficiaries in SEER region; the American Community Survey (ACS), and the Area Health Resource Files (AHRF). SEER program is an epidemiologic surveillance system comprising population-based tumor registries. It collects data on all incident cases of cancer in persons residing in 18 SEER areas. SEER data also encompass information on demographic characteristics, diagnosis date, cancer site, stage, and grade, and type of surgical treatment, and radiation therapy provided (if provided) within four months of diagnosis [126]. Medicare beneficiaries without cancer were identified from the 5% non-cancer sample of these beneficiaries living in same catchment areas as those in SEER program, randomly selected based on the last two digits of their social security number [126]. The individuals who have been reported

to SEER with an incident cancer are removed from this 5% random sample. The information on census-tract level poverty status and education was derived from the ACS [128]. County-level healthcare environment factors (community health clinics, Healthcare Professional Shortage Area (HPSA), and percent of cardiologists and oncologists in the county) were derived from the AHRF [129].

4.3.4 Study Population

The study population comprised beneficiaries with pre-existing CAD and those with incident breast, colorectal, or prostate cancer and those without cancer. CAD was identified using a validated algorithm developed by the Centers for Medicare and Medicaid Services (CMS) [150]. The algorithm used the *International Classifications of Diseases – 9th edition, Clinical Modification* (ICD-9-CM) codes. Individuals with at least two inpatient, outpatient and carrier claims (clinician encounters only), or home health agency service Medicare claims with a primary or secondary diagnosis of CAD during the baseline were classified as having pre-existing CAD. Incident cancer, January 2008 through December 2011, was identified using the *International Classification of Diseases for Oncology, 3rd Edition* (ICD-O-3) codes from the SEER registries. Individuals without cancer were identified from the 5% non-cancer Medicare claims from the SEER regions.

Other inclusion criteria were age 68 years or older, alive with continuous FFS Medicare Part A, B enrollment during the entire study period, continuous part D enrollment during the pre- and post-index period, no missing information on county, who had two or more prescriptions for either statins or two prescriptions for any or combinations of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), or beta-blockers, and total expenditures greater than zero over the two-year period (pre- and post-index period). In the non-cancer cohort, individuals with end-stage renal disease were excluded prior to diagnosis date assignments. In the cancer cohort, individuals with missing data for type and stage of cancer and those who were diagnosed with cancer through autopsy or death certificate were excluded. The selection criteria are presented in

Figure 4.1..

Figure 4.1. Schematic presentation of selection criteria for study cohort.

Abbreviations – CAD: Coronary artery disease; HMO: Health Maintenance Organization

4.3.5 Measures

4.3.5.1 Dependent variable: CAD-related Expenditures

CAD-related healthcare expenditures consisted of Medicare payments for inpatient, home healthcare agency (HHA), and outpatient services for CAD-related care and were measured for every 120 days (t_1 , t_2 , t_3 , t_4 , t_5 , and t_6). CAD-related services were identified using ICD-9-CM primary and secondary diagnosis codes for CAD [198, 199]. Prescription medication and durable medical equipment (DME) expenditures were not included because of the challenges in identifying CAD-related expenditures in DME and prescription drug claims. We also calculated total expenditures for inpatient, home healthcare (HHA), and outpatient services (obtained from outpatient and carrier claims) so that we can calculate the proportion of CAD-related expenditures to total expenditures. The outpatient claims included institutional outpatient services emergency services, laboratory tests, X-rays/other radiology, medical supplies, and preventive/screening services [200]. Carrier claims included physician services and services from other non-institutional providers, such as physician assistants and nurse practitioners [201]. The healthcare expenditures were adjusted by the Consumer Price Index for medical services [202] and expressed in 2012 constant dollars.

4.3.5.2 Key independent Variable – Cancer Type and Sex

As the study included women with breast cancer and men with prostate cancer, our key time-invariant independent variable accounted for both sex and cancer type and was categorized into six mutually exclusive groups: women with breast cancer (BCW), women with colorectal cancer (CCW), women with no cancer (NCW), men with prostate cancer (PCM), men with colorectal cancer (CCM), and men with no cancer (NCM).

4.3.5.3 Other Independent Variables

Predisposing Factors

These were time-invariant and consisted of age in years measured at index month of incident cancer diagnosis and race/ethnicity.

Enabling Factors

These factors Medicare Part D coverage gap (measured every 120 days) and included census tract-level education level and poverty status (measured at baseline). Medicare Part D coverage gap, also referred to as “donut hole” is the phase between the annual coverage limit and catastrophic coverage. Thus, Part D plans start with an annual deductible, after which Medicare pays for the prescription drugs up to an initial coverage limit with certain coinsurance associated with those payments. Prescription drugs are not covered during the period when an individual reaches the annual coverage limit and until the cost of prescription drugs reaches to catastrophic limit [156]. This creates the donut hole.

Need-based Factors

Physical health conditions were measured at baseline and categorized into *concordant* (cardiac arrhythmias, congestive heart failure, diabetes, hyperlipidemia, hypertension, and stroke) and *discordant* (dementia, asthma, chronic obstructive pulmonary disease, arthritis, hepatitis, human immunodeficiency virus, and osteoporosis) conditions. Mental health conditions included severe mental illness (schizophrenia, bipolar disorder, and psychoses) (measured at baseline) and anxiety, and depression (measured every 120 days). For CAD severity, a proxy measure, measured at baseline, was constructed based on the CMS hierarchical condition category (HCC) classification system. Based on the CMS risk adjustment model, each of the HCC codes for CAD was assigned specific score based on the risk and severity [154], ranging from 0.231 to 0.349. Thus, higher scores represented severe manifestations of CAD.

Personal Health Care Practices

This included tobacco use and alcohol abuse as these practices have been reported to negatively affect cardiovascular health [203, 204]. These variables were measured every 120 days.

Healthcare use

This included primary care visits, cardiologist visits, and adherence to statins and/or ACEIs, ARBs, or beta-blockers measured every 120 days. Adherence to these medication classes were defined as proportion of days covered (PDC). It was calculated among only those who filled at least two prescriptions for either statins or any two prescriptions of, ACEIs, ARBs, or beta-blockers. The denominator for PDC was 120 days. For those who were on both statins and ACEIs, ARBs or beta-blockers), PDC was derived by considering the number of days with both classes of medications. Individuals with $PDC \geq 80\%$ were considered as adherent and those with $PDC < 80\%$ were considered as non-adherent [153]. Adherence was classified into five mutually exclusive groups: adherent to both statins and ACEIs/ARBs/beta-blockers, not adherent to both statins and ACEIs/ARBs/beta blockers, adherent to either statins or ACEIs/ARBs/beta-blockers, use of one medication class and adherent to that class, and use of one medication class and not adherent to that medication class.

External Environment Factors

These were time-invariant and measured at baseline. This domain included SEER region – Northeast (Connecticut, New Jersey), South (Kentucky, Louisiana, Atlanta, rural Georgia, and Greater Georgia), North-central (Detroit, Iowa), and West (San Francisco, Hawaii, New Mexico, Seattle, Utah, San Jose, Los Angeles, Greater California), county metro status (based on urban/rural continuum codes from the AHRF), and percentage of cardiologists and oncologists in the county.

In addition to the above-mentioned factors, we also controlled for time (t_1 through t_6) to better reflect for changes with time in treatment practices.

4.3.6 Statistical Analyses

Unadjusted subgroup differences in time-invariant characteristics between cancer and no cancer categories by sex (six groups) were tested with chi-square statistics. Our preliminary analyses indicated that there were significant group differences in age, race/ethnicity, concordant and discordant physical health conditions, mental health conditions, SEER region, and index year between the categories. Therefore, inverse probability treatment weights (IPTW) were derived using the multinomial logistic regression on cancer and no cancer categories. These IPTWs were used when modeling expenditures to adjust for the observed differences between the categories. As seen in **Table 4.1**, such weighting enabled us to balance the difference among the six groups. **Table 4.2** summarizes the findings from the multinomial logistic regression used to calculate IPTW.

Healthcare expenditures have unique features such as: 1) non-negative values; 2) a large number of individuals having zero expenditures; and 3) a small number of individuals having very high expenditures. Therefore, ordinary least squares regression on expenditures is not suitable. An alternative is to transform the expenditures with natural logarithms. With log-transformed expenditures, the impact of cancer on healthcare expenditures reflect percent change in expenditures. Retransformation of the regression coefficients to original dollars involves using smearing-estimators and can become very challenging [205]. Estimating expenditures with generalized linear models (GLM) with appropriate family of distribution and link function can overcome some of these problems [205].

As we measured CAD-related healthcare expenditures every 120 days during pre- and post-index period, each individual had six observations. These six observations were not independent, therefore, we used generalized linear mixed models (GLMM) with gamma distribution and log-link to analyze adjusted relationships between cancer and non-cancer groups and CAD-related healthcare expenditures. This is the most commonly used approach in previous cost analyses [206, 207]. In these GLMMs, predisposing, enabling and need factors as well as external environmental characteristics affecting healthcare expenditures were included. These models also included time as a continuous variable which varied from t_1 through t_6 , and index years with 2008 as the reference group.

Table 4.1. Unweighted and Weighted Percent of Selected Characteristics by Cancer Diagnosis

Characteristics	BCW (%)	CCW (%)	CCM (%)	PCM (%)	NCW (%)	NCM (%)	Sig	BCW (wt. %)	CCW (wt. %)	CCM (wt. %)	PCM (wt. %)	NCW (wt. %)	NCM (wt. %)	Sig
Age groups							***							NS
68-70 years	13.8	9.2	14.7	21.4	13.7	22.4		17.0	16.6	16.7	16.5	16.8	16.9	
71-74 years	19.8	14.5	23.4	30.5	17.2	23.8		20.7	20.8	20.7	20.6	20.6	20.6	
75-79 years	26.0	22.2	25.0	27.8	21.2	23.4		22.8	23.5	23.4	23.0	23.1	22.9	
80 years and older	40.4	54.1	36.9	20.3	47.9	30.4		39.5	39.2	39.2	39.9	39.5	39.6	
Race/Ethnicity							***							NS
Whites	82.5	78.7	82.8	82.7	75.0	77.6		77.5	77.0	77.1	76.0	77.2	77.1	
African Americans	9.4	11.2	4.9	7.6	10.4	5.7		8.7	8.8	8.7	9.0	8.7	8.7	
Hispanics	2.9	2.3	2.1	2.6	4.3	4.0		3.7	3.6	4.1	4.2	3.9	4.0	
Others	5.2	7.8	10.2	7.1	10.3	12.7		10.0	10.6	10.0	10.8	10.2	10.2	
Concordant PHC^a							***							NS
Yes	95.5	96.4	95.4	94.6	94.0	92.4		93.8	93.4	94.0	94.3	93.9	93.9	
No	4.5	3.6	4.6	5.4	6.0	7.6		6.2	6.6	6.0	5.7	6.1	6.1	
Discordant PHC^a							***							
Yes	48.1	51.4	37.5	31.7	50.1	33.9		43.2	43.9	43.4	43.9	43.5	43.8	
No	51.9	48.6	62.5	68.3	49.9	66.1		56.8	56.1	56.6	56.1	56.5	56.2	
MHC^a							***							
Yes	13.0	13.1	8.9	5.7	15.2	9.3		12.1	12.6	12.4	12.6	12.2	12.6	
No	87.0	86.9	91.1	94.3	84.8	90.7		87.9	87.4	87.6	87.4	87.8	87.4	
SEER Region							***							NS
Northeast	24.1	26.3	24.0	20.0	22.7	18.9		21.9	21.6	21.7	20.1	21.6	21.7	
South	25.1	25.4	22.2	24.6	25.6	23.8		24.9	24.5	24.7	25.2	24.7	24.5	
North-central	13.9	14.5	12.8	14.2	11.8	10.5		12.1	11.5	12.1	12.8	12.0	11.9	
West	36.9	33.8	41.0	41.1	39.9	46.8		41.1	42.3	41.5	41.9	41.6	41.9	
Index year							**							NS
2008	24.0	25.1	24.9	24.6	23.9	23.4		24.1	25.9	23.7	22.8	23.9	24.7	
2009	24.5	23.9	23.8	25.1	23.8	24.7		23.8	23.7	24.9	23.6	24.2	24.2	
2010	25.4	25.6	25.3	23.8	26.1	24.8		26.0	25.7	25.6	25.5	25.4	25.2	
2011	26.1	25.3	25.9	26.5	26.3	27.1		26.2	24.7	25.7	28.1	26.6	25.9	

Note: Based on 46,332 elderly fee-for-service Medicare beneficiaries with pre-existing CAD between 2008 and 2011 (12,095 cancer cohort and 34,237 non-cancer cohort).

Individuals with incident breast, colorectal, and prostate cancer were derived from the SEER registries and individuals with no cancer were derived from the 5% non-cancer sample from the SEER region. Weights were derived using the Inverse Probability Treatment Weights approach.

Asterisks represent significant differences in time-invariant patient-level characteristics based on chi-square tests.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$. Column percentages are reported.

Time-invariant characteristics include cancer diagnosis categories, age, race/ethnicity, poverty status, high school education, concordant and discordant physical health conditions, SMI, SEER region, and county-level characteristics. Time-variant characteristics include, tobacco use, alcohol use, depression, anxiety, and routine follow-up with primary care physician and/or cardiologist, and donut hole.

^a Concordant physical health conditions consisted of diabetes, hyperlipidemia, hypertension, stroke, cardiac arrhythmia, and congestive heart failure. Discordant physical health conditions consisted of arthritis, asthma, chronic obstructive pulmonary disease, osteoporosis, dementia, human immunodeficiency virus, and hepatitis. Mental health conditions include anxiety, depression, SMI (schizophrenia, bipolar disorder, and psychoses)

Abbreviations

BCW: Women with breast cancer; CAD: Coronary artery disease; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; FFS: Fee-for-service; MHC: Mental health conditions; NCM: Men with no cancer; NCW: Women with no cancer; PCM: Men with prostate cancer; PHC: Physical health conditions; SEER: Surveillance, Epidemiology and End Results; SMI: Severe mental illness; Wt.: Weighted

Table 4.2. Multinomial Logistic Regression Models used to derive IPTW

Characteristics	BCW			CCW			CCM			PCM			NCW		
	OR	95% CI	Sig	OR	95% CI	Sig	OR	95% CI	Sig	OR	95% CI	Sig	OR	95% CI	Sig
Age groups															
68-70 years	0.48	[0.43, 0.54]	***	0.24	[0.20, 0.28]	***	0.56	[0.47, 0.67]	***	1.45	[1.31, 1.60]	***	0.39	[0.37, 0.42]	***
71-74 years	0.66	[0.60, 0.73]	***	0.36	[0.31, 0.42]	***	0.84	[0.73, 0.98]	*	1.94	[1.77, 2.13]	***	0.47	[0.45, 0.51]	***
75-79 years	0.87	[0.80, 0.96]	**	0.55	[0.49, 0.63]	***	0.91	[0.78, 1.05]		1.81	[1.64, 1.99]	***	0.59	[0.56, 0.63]	***
80 years and older	Ref														
Race/Ethnicity															
African Americans	1.51	[1.32, 1.72]	***	1.93	[1.62, 2.29]	***	0.80	[0.62, 1.04]		1.21	[1.06, 1.38]	**	1.87	[1.71, 2.05]	***
Hispanics	0.7	[0.57, 0.86]	***	0.59	[0.42, 0.83]	**	0.51	[0.35, 0.74]	***	0.65	[0.54, 0.80]	***	1.13	[1.01, 1.27]	*
Others	0.41	[0.35, 0.48]	***	0.72	[0.59, 0.88]	**	0.78	[0.64, 0.95]	*	0.52	[0.46, 0.59]	***	0.93	[0.86, 1.00]	
Whites	Ref														
Concordant PHC															
Yes	1.46	[1.24, 1.73]	***	1.69	[1.29, 2.20]	***	1.61	[1.25, 2.09]	***	1.54	[1.34, 1.78]	***	1.00	[0.92, 1.09]	
No	Ref														
Discordant PHC															
Yes	1.68	[1.56, 1.81]	***	1.82	[1.64, 2.02]	***	1.13	[1.01, 1.27]	*	0.96	[0.89, 1.03]		1.75	[1.67, 1.84]	***
No	Ref														
MHC															
Yes	1.20	[1.07, 1.34]	**	1.19	[1.02, 1.39]	*	0.89	[0.73, 1.09]		0.58	[0.50, 0.66]	***	1.48	[1.37, 1.59]	***
No	Ref														
SEER Region															
Northeast	1.31	[1.19, 1.45]	***	1.58	[1.38, 1.81]	***	1.32	[1.14, 1.54]	***	1.09	[0.99, 1.20]		1.27	[1.20, 1.36]	***
South	1.12	[1.02, 1.24]	*	1.34	[1.16, 1.54]	***	1.02	[0.87, 1.18]		0.99	[0.91, 1.08]		1.24	[1.16, 1.31]	***
North-central	1.41	[1.25, 1.58]	***	1.68	[1.42, 1.98]	***	1.30	[1.08, 1.56]	**	1.35	[1.22, 1.51]	***	1.26	[1.17, 1.36]	***
West	Ref														
Index year															
2008	0.93	[0.84, 1.04]		0.91	[0.78, 1.05]		1.02	[0.87, 1.20]		1.12	[1.02, 1.23]	*	0.89	[0.83, 0.95]	***
2009	0.95	[0.86, 1.05]		0.89	[0.77, 1.03]		0.94	[0.80, 1.10]		1.06	[0.96, 1.16]		0.90	[0.84, 0.96]	***
2010	0.97	[0.87, 1.07]		0.94	[0.82, 1.09]		0.98	[0.84, 1.14]		0.97	[0.89, 1.07]		0.98	[0.92, 1.05]	
2011	Ref														

Note: Based on 46,332 elderly fee-for-service Medicare beneficiaries with pre-existing CAD between 2008 and 2011 (12,095 cancer cohort and 34,237 non-cancer cohort).

Individuals with incident breast, colorectal, and prostate cancer were derived from the SEER registries and individuals with no cancer were derived from the 5% non-cancer sample from the SEER region. Weights were derived using the Inverse Probability Treatment Weights approach.

Asterisks represent significant differences in patient-level characteristics. NCM is the reference category for dependent variable.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$.

Abbreviations

BCW: Women with breast cancer; CAD: Coronary artery disease; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; FFS: Fee-for-service; NCM: Men with no cancer; NCW: Women with no cancer; PCM: Men with prostate cancer; SEER: Surveillance, Epidemiology and End Results; Wt.: Weighted

4.4 Results

4.4.1 Characteristics of the Study Population before and after IPTW Adjustment

The study cohort comprised 46,332 elderly FFS Medicare beneficiaries with pre-existing CAD (12,095 with cancer and 34,237 without cancer). **Table 4.1** summarizes the characteristics of cancer diagnosis categories before and after IPTW adjustment. Prior to adjustment, there were statistically significant differences in age, race/ethnicity, concordant physical conditions, discordant physical conditions, mental health conditions, SEER region, and index year. After adjusting with IPTW, there were no significant differences in these variables between the cancer diagnosis categories.

Table 4.3 summarizes the mean CAD-related and total expenditures during pre- and post-index period. For purposes of this table, expenditures for t₁, t₂, and t₃ were aggregated and represented pre-index period expenditures and expenditures for t₄, t₅, and t₆ were aggregated to represent post-index period. The average CAD-related expenditures ranged from \$3,423 (BCW) to 7,022 (PCM). For all groups, the post-index period expenditures were higher than the pre-index periods. CAD-related expenditures in the post-index period were approximately 3 times higher for CCW and CCM, 2 times for BCW, and 1.5 times for PCM. The post-index CAD-related expenditures for NCM and NCW, in comparison, were similar to those in the pre-index period.

The proportion of CAD-related expenditures ranged from 32.6% (BCW) to 45.8% (NCM) during the pre-index period and 20.8% (BCW) to 46.1% (NCM) during post-index period. Among CCM, the proportion of CAD-related expenditures was the highest during the pre-index period (46.8%) and second highest during post-index period (40.5%).

Table 4.3. Mean and Standard Deviation of Coronary Artery Disease-related Expenditures by Cancer and Non-Cancer Adjusted with IPTW

	Pre-index			Post-index		
	Total Wt. Mean (SD)†	CAD-related Wt. Mean (SD)†	% CAD-related‡	Total Wt. Mean (SD)†	CAD-related Wt. Mean (SD)†	% CAD-related‡
BCW	10,493 (18,644)	3,423 (10,504)	32.6%	29,596 (27,749)	6,154 (14,419)	20.8%
CCW	14,504 (27,138)	5,722 (15,071)	39.5%	55,895 (45,829)	18,916 (27,102)	33.8%
NCW	12,099 (22,579)	4,662 (13,670)	38.5%	10,656 (22,379)	4,164 (13,370)	39.1%
CCM	17,548 (31,452)	8,220 (19,298)	46.8%	56,849 (48,323)	23,021 (28,781)	40.5%
PCM	11,089 (18,689)	4,603 (12,063)	41.5%	28,040 (27,099)	7,022 (16,316)	25.0%
NCM	13,943 (26,758)	6,380 (16,668)	45.8%	11,659 (26,681)	5,377 (15,594)	46.1%

Note: Based on 46,332 elderly fee-for-service Medicare beneficiaries with pre-existing CAD between 2008 and 2011 (12,095 cancer cohort and 34,237 non-cancer cohort).

Individuals with incident breast, colorectal, and prostate cancer were derived from the SEER registries and individuals with no cancer were derived from the 5% non-cancer sample from the SEER region. Weights were derived using the Inverse Probability Treatment Weights approach.

†All expenditures reported in 2012 USD, ‡Percentage CAD-related = $\frac{\text{CAD-related expenditures}}{\text{Total expenditures}} \times 100$

Abbreviations

BCW: Women with breast cancer; CAD: Coronary artery disease; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; FFS: Fee-for-service; IPTW: Inverse Probability Treatment Weights; NCM: Men with no cancer; NCW: Women with no cancer; PCM: Men with prostate cancer; SEER: Surveillance, Epidemiology and End Results, Wt.: Weighted

4.4.2 CAD-related Expenditures over time by Cancer and Non-Cancer Status

Figure 4.2 displays CAD-related expenditures over time for cancer and non-cancer groups. When time was included as an adjustor, the time coefficient was positive across all cancer group, suggesting that CAD-related expenditures increased over time for all cancer groups. However, no such differences were observed for non-cancer groups.

4.4.3 Adjusted Relationships between Cancer and CAD-related Healthcare Expenditures

Beta coefficient, standard error (SE), percent change, from the adjusted GLMM with gamma distribution and log link are presented in **Table 4.4** (total CAD-related expenditures) and **Table 4.5** (inpatient and outpatient CAD-related expenditures). Because the cancer and non-cancer groups were grouped by sex, we present CAD-related expenditures with the following contrasts: cancer versus no cancer, women versus men and cancer type (breast cancer versus women with colorectal cancer and prostate cancer versus men with colorectal cancer).

4.4.3.1 Cancer versus No cancer and CAD-related Healthcare Expenditures

After controlling for all the independent variables and time, mentioned in the methods section, and with NCW as the reference group, both BCW and CCW groups had 14% and 151% higher expenditures, respectively. With NCM as the reference group, both CCM and PCM had 164% and 12% higher expenditures, respectively.

With NCW as the reference group, CCW had 239% higher inpatient CAD-related expenditures. There was no significant difference between BCW and NCW for inpatient CAD-related expenditures. However, compared to NCW, both BCW and CCW had 54% and 48% significantly higher outpatient CAD-related expenditures, respectively.

Similarly, with NCM as the reference group, CCM had 249% significantly higher inpatient CAD-related expenditures compared to NCM. There was no significant difference between PCM and NCM for inpatient CAD-related expenditures. However, compared to NCM, both CCM and PCM had 51% and 31% significantly higher outpatient CAD-related expenditures, respectively.

4.4.3.2 Sex and CAD-related Healthcare Expenditures

When examined by sex, healthcare expenditures were 21% lower among NCW compared to NCM; CCW had 25% lower expenditures compared to CCM. Similarly, NCW and CCW had lower inpatient and outpatient expenditures compared to NCM and CCM, respectively.

4.4.3.3 Cancer Type and CAD-related Healthcare Expenditures

Healthcare expenditures were 55% higher among CCW compared to BCW. Similarly, healthcare expenditures were 57% higher among CCM compared to PCM. Further, CCW and CCM had 67% and 68% higher inpatient CAD-related expenditures compared to BCW and PCM, respectively. However, there was no significant difference between CCW and BCW as well as CCM and PCM for outpatient healthcare expenditures.

Figure 4.2. Weighted Average CAD-related Expenditures among Cancer and Non-cancer Cohorts across 120-day intervals

Note: Based on 46,332 elderly fee-for-service Medicare beneficiaries with pre-existing CAD between 2008 and 2011 (12,095 cancer cohort and 34,237 non-cancer cohort).

Individuals with incident breast, colorectal, and prostate cancer were derived from the SEER registries and individuals with no cancer were derived from the 5% non-cancer sample from the SEER region. Weights were derived using the Inverse Probability Treatment Weights approach.

Asterisks represent significant differences in cancer and non-cancer groups.

*** $p < 0.001$; ** $0.001 \leq p < 0.01$; * $0.01 \leq p < 0.05$

Abbreviations

BCW: Women with breast cancer; CAD: Coronary artery disease; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; FFS: Fee-for-service; NCM: Men with no cancer; NCW: Women with no cancer; PCM: Men with prostate cancer; SEER: Surveillance, Epidemiology and End Results; Wt.: Weighted

Table 4.4. Parameter Estimates from Generalized Linear Mixed Models on CAD-related Expenditures with IPTW

Cancer dx categories	Coefficient	Std error	P value	% change
Cancer versus non-cancer differences in expenditures (Reference: NCW)^a				
BCW	0.13	0.04	0.002	14%
CCW	0.92	0.05	0.000	151%
Intercept	4.01	0.14		
Cancer versus non-cancer differences in expenditures (Reference: NCM)^b				
CCM	0.97	0.05	0.000	164%
PCM	0.11	0.04	0.008	12%
Intercept	4.25	0.14		
Sex differences in expenditures (Reference: NCM)^c				
NCW	-0.24	0.03	0.000	-21%
Intercept	4.25	0.14		
Sex differences in expenditures (References: CCM)^d				
CCW	-0.29	0.07	0.000	-25%
Intercept	5.22	0.15		
Cancer type differences in expenditures (Reference: BCW)^e				
CCW	0.79	0.06	0.000	55%
Intercept	4.93	0.15		
Cancer type differences in expenditures (Reference: PCM)^f				
CCM	0.85	0.06	0.000	57%
Intercept	5.22	0.15		

Note: Based on 46,332 elderly fee-for-service Medicare beneficiaries with pre-existing CAD between 2008 and 2011 (12,095 cancer cohort and 34,237 non-cancer cohort).

Individuals with incident breast, colorectal, and prostate cancer were derived from the SEER registries and individuals with no cancer were derived from the 5% non-cancer sample from the SEER region. Weights were derived using the Inverse Probability Treatment Weights approach. Adjusted models controlled for time, predisposing, enabling, need, healthcare behavior, healthcare use, and environmental factors.

Significance was derived from adjusted generalized linear model with Gamma distribution and log-link. The analysis used 6 repeated measures.

% Change for GLMM was calculated as $(e^{(\text{intercept} + \beta)} - e^{\text{intercept}}) / e^{\text{intercept}}$.

^a Other categories not displayed are: CCM, PCM, and NCM.

^b Other categories not displayed are: BCW, CCW, and NCW.

^c Other categories not displayed are: BCW, CCW, CCM, and PCM.

^d Other categories not displayed are: BCW, PCM, NCW, and NCM.

^e Other categories not displayed are: CCM, PCM, NCW, and NCM.

^f Other categories not displayed are: BCW, CCW, NCW, and NCM.

Abbreviations

BCW: Women with breast cancer; CAD: Coronary artery disease; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; FFS: Fee-for-service; GLMM: Generalized linear mixed models; IPTW: Inverse Probability Treatment Weights; NCM: Men with no cancer; NCW: Women with no cancer; PCM: Men with prostate cancer; SE: Standard error; SEER: Surveillance, Epidemiology and End Results; Wt.: Weighted

Table 4.5. Parameter Estimates from Generalized Linear Mixed Models on CAD-related Expenditures with IPTW

Cancer dx categories	Inpatient CAD-related expenditures				Outpatient CAD-related expenditures			
	Coefficient	Std error	P value	Change	Coefficient	Std error	P value	Change
Cancer versus non-cancer differences in expenditures (Reference: NCW)^a								
BCW	0.11	0.08	0.15	12%	0.43	0.04	0.000	54%
CCW	1.22	0.08	0.000	239%	0.39	0.05	0.000	48%
Intercept	2.36	0.20			3.13	0.12		
Cancer versus non-cancer differences in expenditures (Reference: NCM)^b								
CCM	1.25	0.08	0.000	249%	0.41	0.06	0.000	51%
PCM	0.10	0.07	0.152	11%	0.27	0.04	0.000	31%
Intercept	2.71	0.20			3.47	0.11		
Sex differences in expenditures (Reference: NCM)^c								
NCW	-0.35	0.06	0.000	-30%	-0.35	0.03	0.000	-30%
Intercept	2.71	0.20			3.47	0.11		
Sex differences in expenditures (Reference: CCM)^d								
CCW	-0.38	0.10	0.000	-32%	-0.37	0.07	0.000	-31%
Intercept	3.96	0.21			3.89	0.13		
Cancer type differences in expenditures (Reference: BCW)^e								
CCW	1.11	0.1	0.000	67%	-0.04	0.06	0.522	-4%
Intercept	3.58	0.21			3.52	0.13		
Cancer type differences in expenditures (Reference: PCM)^f								
CCM	1.14	0.09	0.000	68%	0.14	0.09	0.056	13%
Intercept	3.96	0.21			3.89	0.13		

Note: Based on 46,332 elderly fee-for-service Medicare beneficiaries with pre-existing CAD between 2008 and 2011 (12,095 cancer cohort and 34,237 non-cancer cohort).

Individuals with incident breast, colorectal, and prostate cancer were derived from the SEER registries and individuals with no cancer were derived from the 5% non-cancer sample from the SEER region. Weights were derived using the Inverse Probability Treatment Weights approach. Adjusted models controlled for time, predisposing, enabling, need, healthcare behavior, healthcare use, and environmental factors.

^aOther categories not displayed are: CCM, PCM, and NCM.

^bOther categories not displayed are: BCW, CCW, and NCW.

^cOther categories not displayed are: BCW, CCW, CCM, and PCM.

^dOther categories not displayed are: BCW, PCM, NCW, and NCM.

^eOther categories not displayed are: CCM, PCM, NCW, and NCM.

^fOther categories not displayed are: BCW, CCW, NCW, and NCM.

Significance was derived from adjusted generalized linear model with Gamma distribution and log-link. The analysis used 6 repeated measures.

% Change for GLMM was calculated as $(e^{(\text{intercept} + \beta)} - e^{\text{intercept}})/e^{\text{intercept}}$.

Abbreviations

BCW: Women with breast cancer; CAD: Coronary artery disease; CCM: Men with colorectal cancer; CCW: Women with colorectal cancer; FFS: Fee-for-service; IPTW: Inverse Probability Treatment Weights; NCM: Men with no cancer; NCW: Women with no cancer; PCM: Men with prostate cancer; SEER: Surveillance, Epidemiology and End Results; Wt.: Weighted

4.4.4 Relationship between Other Independent Variables and Expenditures

Table 4.6 displays regression coefficient, standard errors, and *P* values of other independent variables from the adjusted GLMM models. Factors associated with significantly increased expenditures included age ≥ 80 years, concordant and discordant physical health conditions, mental health conditions, higher CAD severity, tobacco use, alcohol use, those with primary care physician or cardiologist visit, and those not adherent to one or both medication classes (for those using both medication classes).

Table 4.6. Adjusted Relationship between Other Characteristics and CAD-related Expenditures, Repeated Measures Regressions with IPTW

Characteristics	β	SE	P value
Predisposing factors			
Age groups (in years)			
68-70	-0.50	0.04	0.000
71-74	-0.48	0.04	0.000
75-79	-0.35	0.03	0.000
≥ 80	Ref		
Race/Ethnicity			
Whites	0.33	0.05	0.000
African Americans	0.79	0.07	0.000
Hispanics	0.31	0.08	0.000
Others	Ref		
Enabling factors			
Education level			
Less than national avg 12%	0.06	0.03	0.031
GE national avg 12%	Ref		
Poverty level			
Less than national avg 14.3%	-0.03	0.03	0.262
GE national avg 14.3%	Ref		
Donut hole			
Not reached	-0.35	0.05	0.000
Reached	0.06	0.06	0.337
Exceeded	Ref		
Need factors			
Concordant PHCs ^a			
Yes	0.64	0.08	0.000
No	Ref		
Discordant PHCs ^a			
Yes	0.39	0.03	0.000
No	Ref		
Mental health conditions ^a			
Yes	0.74	0.03	0.000
No	Ref		
CAD severity	0.80	0.06	0.000
Health behavior			
Tobacco use			
Yes	0.36	0.05	0.000
No	Ref		
Alcohol use			
Yes	0.43	0.11	0.000
No	Ref		
Healthcare use			
Primary care visit			
Yes	1.23	0.03	0.000
No	Ref		
Cardiologist visit			
Yes	1.96	0.02	0.000
No	Ref		
Adherence to medication			
No ADH 2 Rx	0.55	0.04	0.000
ADH 1 of 2 Rx	0.22	0.03	0.000
ADH 1 Rx	-0.18	0.04	0.000

No ADH 1 Rx	0.25	0.04	0.000
ADH 2 Rx	Ref		
External Environment and County-level Factors			
SEER Region			
Northeast	-0.25	0.05	0.000
South	-0.02	0.05	0.710
North-central	-0.12	0.05	0.010
West	Ref		
Metropolitan status			
Metro	-0.25	0.04	0.000
Non-metro	Ref		
HPSA			
No shortage	-0.05	0.05	0.276
Part county	0.13	0.03	0.000
Whole county	Ref		
FQHC			
None	0.04	0.06	0.510
1 to 10	0.06	0.04	0.119
GE 11	Ref		
Rural health centers			
Yes	0.02	0.03	0.534
No	Ref		
Time	0.02	0.01	0.000

Note: Based on 46,332 elderly fee-for-service Medicare beneficiaries with pre-existing CAD between 2008 and 2011 (12,095 cancer cohort and 34,237 non-cancer cohort).

Individuals with incident breast, colorectal, and prostate cancer were derived from the SEER registries and individuals with no cancer were derived from the 5% non-cancer sample from the SEER region. Weights were derived using the Inverse Probability Treatment Weights approach.

Time-invariant characteristics include cancer diagnosis categories, age, race/ethnicity, poverty status, high school education, concordant and discordant physical health conditions, SMI, SEER region, and county-level characteristics. Time-variant characteristics include, tobacco use, alcohol use, depression, anxiety, and routine follow-up with primary care physician and/or cardiologist, and donut hole.

^aConcordant physical health conditions consisted of diabetes, hyperlipidemia, hypertension, stroke, cardiac arrhythmia, and congestive heart failure. Discordant physical health conditions consisted of arthritis, asthma, chronic obstructive pulmonary disease, osteoporosis, dementia, human immunodeficiency virus, and hepatitis. Mental health conditions include anxiety, depression, SMI (schizophrenia, bipolar disorder, and psychoses)

Significance was derived from adjusted generalized linear model with Gamma distribution and log-link. The analysis used 6 repeated measures.

Abbreviations

ADH 2 Rx: Adherent to both statins and ACEIs/ARBs/beta-blockers;

No ADH 2 Rx: Not adherent to both medication classes

ADH 1 of 2 Rx: Adherent to either statins or ACEIs/ARBs/beta-blockers;

ADH 1 Rx: Use of one medication class and adherent to that class;

No ADH 1 Rx: Use of one medication class and not adherent to that medication class;

Abbreviations:

ACEIs: Angiotensin-converting enzyme inhibitors; ARBs: Angiotensin II receptor blockers; CAD: Coronary artery disease; FFS: Fee-for-service; IPTW: Inverse Probability Treatment Weights; PHC: physical health conditions; SE: Standard error; SEER: Surveillance, Epidemiology and End Results; Wt.: Weighted

4.5 Discussion

To date, this is amongst the first study to estimate CAD-related expenditures among cancer and non-cancer FFS Medicare beneficiaries with pre-existing CAD and analyze the relationship between incident cancer diagnosis and short-term CAD-related (inpatient and outpatient) expenditures. In general, CAD accounted for 32.6% to 46.8% of total expenditures during pre-index period and 20.8% to 46.1% during the post-index period among cancer patients. These findings suggest that a substantial portion of total expenditures accounted for care that is directly related to CAD.

Our study findings suggest that CAD-related expenditures were higher among those with cancer than those without cancer. We speculate that part of the CAD-related expenditures among patients with cancer may have resulted from cancer treatments [60, 61, 72]. Moreover, it is plausible that cancer may take precedence over CAD management and impede the recommended care for CAD, thereby increasing CAD-related complications [69] leading to higher CAD-related expenditures. For patients undergoing cancer surgery, CAD may need to be stabilized using medical management [72], further adding to the overall CAD-related expenditures among cancer patients.

A noteworthy finding is that CAD-related expenditures were highest among elderly with colorectal cancer compared to breast cancer or prostate cancer or no cancer. We observed that CAD-related expenditures were highest during 120 days immediately after colorectal cancer diagnosis. We also found that a majority of patients had advanced stage (63.0%) colorectal cancer. Colorectal cancer treatments primarily consist of surgery and adjuvant chemotherapy (e.g., 5-fluorouracil and capecitabine) for those with Stages II- IV [67]. Taken together, these findings suggest that CAD-related expenditures may be higher among those with colorectal cancer due to chemotherapy-related cardiotoxicity. Our preliminary study findings demonstrated that non-adherence to statins and ACEIs/ARBs/beta-blockers was significantly higher in colorectal cancer patients who had surgery (81% in this study). Non-adherence to these medications has been previously shown to increase the risk of CAD-related complications and hospitalizations, thereby increasing inpatient expenditures [94].

CAD-related expenditures increased over time for all cancer groups. A closer examination of the study findings indicated that CAD-related expenditures were highest during the 120-day interval immediately after cancer diagnosis, suggesting that the period after cancer diagnosis may be the crucial in terms of monitoring and management of CAD.

Our study findings have significant implications for the policy makers and insurance providers. The Centers for Medicare and Medicaid Services' has rolled out demonstration projects for new bundled payment models that support payments for episodes of care [193]. Similarly, the Medicare's shared savings program provides Accountable Care Organizations financial incentives to reduce spending and improve quality [208]. These programs use risk adjustment and also calculate expenditure benchmarks needed to provide care and get shared savings from the CMS. Collectively, our findings can help the payers to calculate these benchmark expenditures by adjusting for case-mix of Medicare beneficiaries, specifically those with pre-existing CAD and incident cancer [194-196]. In addition, our findings can help capture the episode-specific contribution of individual risk factors (age, gender, comorbidities, episode severity, etc.) to resource use similar to those implemented by the PROMETHEUS payment models [196, 209]. Currently, there are no specific payment models that account for cancer and CAD, but available

models, such as PROMETHEUS can be tailored to the specific patterns of resource use within CAD. Therefore, it is crucial to understand the extent to which a specific cancer contributes to CAD-related expenditures to implement these models. Based on our study findings, it is apparent that resource allocation for CAD-related expenditures should be higher for those with colorectal cancer, followed by prostate and breast cancer.

We also found that CAD-related inpatient expenditures accounted for two-thirds of the overall CAD-related health care expenditures. Although CMS has imposed penalties for potential hospital readmissions and preventable hospitalizations, such as inpatient admissions for angina without procedures [210], these initiatives may not be effective in patients with complex conditions such as CAD and cancer. In this context, future research needs to focus on collaborative care models such as the patient-centered medical home (PCMH) because such models have been shown to reduce inpatient use. For example, a review focusing on patient-centered medical home (PCMH) indicated that PCMH was associated with reduction in inpatient hospital expenditures [211]; Geisinger Health System's patient-centered medical home clinics reported 18.6% cost savings for inpatient care, the largest contributor to the total cost savings [212].

Another noteworthy finding was that women had lower CAD-related expenditures compared to men. Chiha et al. assessed the differences in CAD severity among men and women and noted that women were more likely to have normal coronary arteries or less severe disease than age-matched men [213]. Although we controlled for severity of CAD with HCC, future research needs to explore whether the lower expenditures among women are due to sex differences in severity of CAD.

4.5.1 Strengths and limitations

This study adopted a longitudinal design and compared expenditures over time between cancer and non-cancer groups. We also used statistical adjustment for selection bias in observed and unobservable characteristics. The use of Medicare FFS claims data enabled us to track individuals across various providers and settings and calculate expenditures and measure variables for specific time periods. The study also adjusted a comprehensive list of factors that can influence CAD-related expenditures. The study included individuals with significant medical comorbidities.

Our study findings need to be interpreted in the context of its limitations. The study findings cannot be generalized to all Medicare beneficiaries because the study population is restricted to those residing in SEER regions and to those with FFS Medicare plans. Further, the SEER-Medicare data are not developed for research purposes and therefore have limitations associated with its use for estimating healthcare expenditures. It is possible that CAD diagnosis may be under-coded or misclassified in claims data, as these data are dependent on professional ICD coding. Therefore, there might be underestimation of CAD-related diagnosis, which in turn, may undermine CAD-related expenditures. Finally, we were not able to control for patient-level lifestyle health behaviors, knowledge, attitude, and preferences as well as number of cancer-related complications, treatment side-effects, and cost-related factors that may affect CAD-related expenditures.

4.5.2 Conclusions

Our study provided unique information and contributed to the nascent literature on cardio-oncology by comparing CAD-related expenditures among elderly FFS Medicare beneficiaries with and without cancer. We found that incident cancer diagnosis was associated with higher short-term CAD-related expenditures as compared to those with no cancer diagnosis. Specifically, inpatient expenditures for colorectal cancer patients were considerably higher than outpatient expenditures. This suggests that more emphasis is warranted on preventing cardiac events in the outpatient setting in order to reduce the more expensive inpatient encounters. Future studies need to explore whether the emerging payment reforms and collaborative care models can lower costs while maintaining high quality CAD care for patients with and without cancer.

Chapter 5

Discussion of Findings and Research Implications

5.1 Summary of Findings and Discussion

Coronary artery disease (CAD) is one of the most burdensome chronic conditions in the elderly [4, 12, 24, 25, 27]. The two key goals of long-term management of CAD are (i) to reduce symptoms and ischemia and (ii) prevent myocardial infarction and death, by lowering lipids and blood pressure [29]. Of all the risk reduction strategies, use and adherence to concomitant pharmacotherapy with statins and beta-blockers, angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) have been shown to be highly effective and has become the cornerstone of CAD management. However, adherence to concomitant pharmacotherapy can be influenced by many factors including the development of other life-threatening conditions such as cancer. The presence of CAD and incident cancer is a prototype example of AHRQ definition of a complex chronic illness “two or more chronic conditions in which each condition might influence the care of the other condition, either through a limitation on life expectancy imposed by one of the conditions or because these two conditions generally entail therapies which are likely to have interactions with each other, or thirdly wherein one of these conditions might be requiring therapies that are contraindicated by the presence of the other conditions” [73]. To date, no real-world study has assessed how incident cancer can affect adherence to concomitant pharmacotherapy and whether concomitant pharmacotherapy can minimize the negative effects of some cancer treatments on CAD-related morbidity and expenditures among individuals with CAD and incident cancer.

The subsequent presence of incident cancer among individuals with CAD is especially important for many reasons: (i) CAD and cancer have shared risk factors and unique pathophysiology; (ii) adults with CAD are more likely to develop cancer; (iii) there can be negative effects of some cancer treatments on cardiovascular health; (iv) as both CAD and cancer are life-threatening conditions, the co-management of these conditions is especially challenging; and (v) both conditions are very costly to treat and manage and such heavy financial burden has implications for payers, healthcare providers and patients.

Cardio-oncology or onco-cardiology is an emerging field and most of the existing evidence on management of heart diseases in individuals with cancer is based on the clinical expert opinion. However, there is paucity of studies on the influence of cancer diagnosis on management of CAD. The current study contributes to the nascent literature on management of CAD in patients with cancer. This study focused on 1) association between incident breast, colorectal, and prostate cancer diagnosis and adherence to statins and/or ACEIs/ARBs/beta-blockers among elderly fee-for-service (FFS) Medicare beneficiaries with pre-existing CAD; 2) the impact of non-adherence to these medication classes on short-term CAD-related hospitalizations in patients with incident cancer diagnosis; and 3) the impact of incident cancer diagnosis on short-term CAD-related inpatient and outpatient healthcare expenditures.

We observed that both men and women diagnosed with incident colorectal cancer were less likely to adhere to both statins and ACEIs/ARBs/beta-blockers compared to non-cancer women and men, even after controlling for a comprehensive list of factors. In addition, men with incident prostate cancer were less likely to adhere to both

medication classes, but the magnitude of difference was much less compared to men with no cancer. There were no differences in adherence to both medication classes by presence of breast cancer. Taken together, these findings suggest that cancer type rather than cancer itself may affect medication adherence. Furthermore, we also found that among Medicare beneficiaries with CAD and colorectal cancer, those with late-stage cancer compared to early stage cancer and those who had surgical treatment for cancer compared to no surgical treatment were less likely to be adherent to both statins and ACEIs/ARBs/beta-blockers. These findings suggest that cancer stage and cancer treatment may affect medication adherence among colorectal cancer patients.

These findings from our study highlight the difficulty in sustaining ongoing therapy for CAD among these individuals and their vulnerability to CAD-related complications. Extant literature shows that non-adherence to statins and ACEIs/ARBs/beta-blockers has negative cardiovascular health consequences, including cardiovascular events and hospitalization [94-96]. Further evidence suggests an increase in the risk of first hospitalization for CAD during the six months after cancer diagnosis [171], perhaps due to cardiotoxicity associated with cancer treatments such as radiotherapy, chemotherapy, and hormone therapy [60-62]. We analyzed the relationship between adherence to both statins and ACEIs/ARBs/beta-blockers and CAD-related hospitalizations among the elderly Medicare beneficiaries with pre-existing CAD and incident breast, colorectal, or prostate cancer.

Compared to Medicare beneficiaries with CAD and cancer who were adherent to both statins and ACEIs/ARBs/beta-blockers, those who were non-adherent to either both or single medication classes were more likely to have CAD-related hospitalization. We also observed that CAD-related hospitalizations increased in the period immediately following cancer diagnosis for all medication adherence categories. Our findings are consistent with the published literature (not specific to cancer) that non-adherence to statins and ACEIs/ARBs/beta-blockers have negative cardiovascular health consequences [94-96].

Coronary artery disease is ranked first in healthcare expenditures, with an estimated \$231.1 billion (2013) [186]. A large proportion of these expenditures can be attributed to CAD-related hospitalizations and outpatient care [188]. For the individuals with incident cancer diagnosis, CAD-related expenditures can be higher than those with only CAD [189] as specific cancer treatments may worsen pre-existing CAD and cancer treatment may, dominantly, impede the continual management of CAD. We analyzed the impact of incident cancer on CAD-related expenditures within our study population.

Our findings suggest that CAD accounted for substantial proportion of total expenditures, i.e., ranging from 32.6% to 46.8% at pre-index period. These are similar to the findings from existing studies [186], which suggest that CAD is one of the most expensive chronic conditions. In addition, CAD-related expenditures were higher among those with cancer than those without cancer. We can speculate that higher CAD-related expenditures among patients with cancer can be due to pre-existing cardiac health, resulting from cancer treatments [60, 61, 72].

Surprisingly, CAD-related expenditures were highest among elderly with colorectal cancer and significantly higher for colorectal cancer compared to breast cancer or prostate cancer. We observed that CAD-related expenditures were highest during 120 days immediately following colorectal cancer diagnosis. We also found that a majority of patients had advanced stage (63.0%) colorectal cancer. The treatment for colorectal cancer primarily consists of surgery and adjuvant chemotherapy (e.g., 5-fluorouracil and capecitabine) for those with Stages II- IV

[67]. It has been reported that patients receiving 5-fluorouracil have 45% risk of angina and 22% risk of MI [67]. Taken together, these findings suggest that CAD-related expenditures may be higher among those with colorectal cancer due to chemotherapy-related cardiotoxicity, interference from cancer treatment, and/or non-adherence to CAD medications. Noticeably higher inpatient expenditures in our study for those with colorectal cancer compared to non-cancer or other cancer (breast and prostate) groups can be attributed to increase in CAD-related complications in these patients. Our study findings also demonstrated that the time coefficient was positive across all cancer groups and no such difference was observed for non-cancer groups. This suggests that CAD-related expenditures increased over time for all cancer groups. A closer examination of the study findings indicated that CAD-related expenditures were highest during the 120-day interval immediately after cancer diagnosis. This suggests that the period after cancer diagnosis is the crucial period for co-management of CAD and cancer.

Together, our study findings suggest that cancer diagnosis negatively impacts adherence to CAD pharmacotherapy. Reduction in adherence was associated with increase in CAD-related hospitalizations and subsequent increase in CAD-related expenditures. Our study findings warrant the integration of cardiovascular care in the elderly diagnosed with cancer.

5.2 Clinical Implications of the Findings

5.2.1 Clinical Implications

Both CAD and cancer are life-threatening conditions and co-management of both conditions can be challenging. Lack of effective management of CAD may not only increase CAD complications, but can also have negative consequences for cancer prognosis. Current clinical practices recommend stabilizing pre-existing CAD prior to initiating cancer treatment. For example, appropriate pharmacologic management (statins and beta-blockers) of the patient with pre-existing CAD is recommended for those undergoing cancer surgery [72]. In addition, statins and ACEIs/ARBs/beta-blockers are central to improving CAD-related health outcomes. Statins have been shown to reduce cancer-specific mortality in those with breast, colorectal, and prostate cancer [144-146, 164]. Further, medications for CAD may also reduce cancer treatment-related cardiotoxicity [71]. Given the complexity of interaction between CAD and cancer, it is important to routinely monitor medication adherence in general clinical practice and provide linkages to support services that can increase medication adherence.

Medication adherence is a multidimensional issue in which providers, patients, payers, and policy makers are inextricably linked and all of them need to be involved in improving medication adherence [165]. It may be very challenging for clinicians to implement interventions in routine practice because those successful-to-date have included multiple, heterogeneous components [141]. In this context, the recent healthcare delivery models such as the medical home may help in overcoming the challenges to coordination across different providers. It has been shown that patient-centered medical homes can improve adherence to medications among those with cardiovascular conditions [166]. Therefore, an interdisciplinary and integrated approach to cardiovascular management in the elderly diagnosed with incident cancer, such as the burgeoning cardio-oncology clinics, would improve cardiovascular outcomes [183].

5.2.2 Policy Implications

Recognition and management of CAD alongside cancer care are pivotal priorities. Our study findings have several policy implications. First, examination of adherence to statins and ACEIs/ARBs/beta-blockers among the elderly is important for policy purposes because Medicare provides coverage for almost all of the elderly in the US [99] and Medicare payments for CAD [100] and cancer care [101] are substantial. Our study findings highlight the need for practice and policy measures to increase CAD management, especially adherence to CAD pharmacotherapy among elderly diagnosed with incident colorectal cancer. However, under the FFS programs, there are no incentives to coordinate care across multiple systems, providers, and payers [141]. In this context, the new fiscal incentives by the CMS in paying physicians who provide care for patients with multiple chronic conditions and who invest time and resources to provide more coordinated and patient-centered care [161] may also promote adherence. It has to be noted that a systematic review of medication adherence among those with multiple chronic conditions reported that medication adherence interventions were “almost exclusively” conducted by the pharmacists [162]. In recognition of the critical role of pharmacists, Medicare now covers Medication Management Services (MTM) of pharmacists. Therefore, implementation of such policies among CAD patients can improve adherence [163].

Second, policy measures have also focused on reducing CAD-related hospitalizations, specifically readmission and preventable hospitalizations. The Affordable Care Act, under Hospital Readmissions Reduction Program, provided CMS the authority to reduce payments to hospital readmissions for certain conditions (heart failure, myocardial infarction, and pneumonia) that it deemed avoidable [184]. CMS has imposed penalties for potential hospital readmissions and preventable hospitalizations, such as inpatient admissions for angina without procedures [210], these initiatives may not work in patients with complex conditions such as CAD and cancer and alternative models may be needed to reduce inpatient expenditures. In addition, based on AHRQ’s prevention quality indicators, hospitalizations related to conditions, such as angina without procedure and congestive heart failure, are considered preventable hospitalizations with good outpatient care. Therefore, it is important to implement policies focusing on integrated care for patients with pre-existing CAD and incident cancer diagnosis in order to reduce avoidable hospitalizations. Future research needs to focus on collaborative care models such as the patient-centered medical home because such models have been shown to reduce inpatient use. A review focusing on patient-centered medical home (PCMH) indicated that PMCH was associated with reduction in inpatient hospital expenditures [211]. For example, Geisinger Health System’s patient-centered medical home clinics showed 18.6% cost savings for inpatient care, the largest contributor to the total cost savings [212].

Third, estimating the extent to which incident cancer affects CAD-related expenditures can help the payers with the emerging healthcare delivery reform initiatives, which are focused on financial incentives to improve healthcare quality with lower healthcare expenditures. New payment models from the CMS support bundled payments to clinicians for providing care to patients with CAD [193]. Such models have the potential to be extended to those who develop cancer after CAD. In addition, estimating payments for CAD-related care may also help providers because the Medicare Access and Children’s Health Insurance Program Reauthorization Act of 2015 (MACRA; payment reform by Medicare) has created alternative payment models [193]. Similarly, the Medicare’s shared savings program provides Accountable Care Organizations financial incentives to reduce spending and improve

quality [208]. These programs use risk adjustment while also setting the expected expenditure benchmark for individuals with pre-existing CAD and incident cancer diagnosis [194-196]. For example, bundled payment model, PROMETHEUS, creates different risk adjustment models for each episode of care, where each model captures the episode-specific contribution of individual risk factors (age, gender, comorbidities, episode severity, etc.) to resource use [196, 209]. Understanding the extent to which a specific cancer contributes to CAD-related expenditures can tailor such models to the specific patterns of resource use within CAD.

5.3 Unique Contributions of the Study

There are several facets of our study that makes it unique. First, it fills a critical knowledge gap on the management of chronic conditions among patients with incident cancer diagnosis. It is important to recognize ways in which cancer could affect the management of pre-existing CAD in cancer patients so that patient-centered care and individualized treatment can be achieved. Second, the study findings can illuminate the complex relationship between CAD management and incident cancer. Prior studies have suggested that cardiovascular disease management is compromised in cancer patients. Third, this study is a population-based study utilizing “real-world” data. It has been pointed out by the investigators of the CLARIFY study that real-world studies on CAD are warranted because “clinical trials or registries which often have stringent exclusion criteria, and do not adequately represent populations with stable CAD (in terms of age, comorbidity, and concomitant therapy)”. This study is the next best alternative to clinical trials for understanding this relationship. Fourth, this dissertation focuses on elderly population and it is estimated that by 2050, there will be 83.7 million over the age of 65. More importantly, both CAD and cancer are highly prevalent in aging population. An understanding of the influence of life events such as cancer diagnosis on management of pre-existing CAD is important to the growing elderly population with these chronic conditions. Lastly, this study focuses on elderly FFS Medicare beneficiaries. Medicare is the primary payer of healthcare for elderly in the US and bears the largest share of the clinical, humanistic, and economic burden in this population. The findings from this study will have implications for the various healthcare delivery and financing reforms such as the establishment of accountable care organizations, patient-centered medical home and others undertaken by the Centers for Medicare and Medicaid Services, which is responsible for setting policy priorities and healthcare payments.

5.4 Strengths and Limitations of the Study

5.4.1 Study Strengths

The study has several strengths. First, a robust repeated measures study design was used comparing a large cohort of cancer and non-cancer cohort over a long period of time across a variety of providers. Further, the study used a variety of statistical methods to control for both observed and unobserved selection bias to ensure robustness of findings. Second, Medicare FFS claims data aided in the measurement of adherence over time and followed a large cohort of patients for a long period of time across a variety of providers. Third, the study adjusted a comprehensive list of factors that can influence medication adherence. Fourth, the study included individuals with

significant medical comorbidities, typically excluded from randomized clinical trials and examined real-world practice patterns.

5.4.2 Study Limitations

The study findings need to be interpreted in the context of its limitations. First, the study findings cannot be generalized to all Medicare beneficiaries because the study population is restricted to those residing in SEER regions and to those with FFS Medicare plans. It is anticipated that those with health maintenance organization plans may receive improved quality of care, hence, the study might have underestimated adherence and may have overestimated hospitalizations and expenditures by focusing only on FFS Medicare beneficiaries. Further, the study population was restricted to elderly population with breast, colorectal, or prostate cancer and pre-existing CAD. Second, a proxy measure was used for CAD severity, which may not reflect the precise CAD severity in the population. Gold standards for measuring CAD severity, such as stress tests, are not available in Medicare database. Also, with claims database, it is not possible to determine how cancer was confirmed. Third, the study did not control for patient-level lifestyle health behaviors, knowledge, attitude, and preferences as well as number of cancer-related complications, treatment side-effects, and cost-related factors that may affect adherence as well as hospitalizations. However, a comprehensive list of variables was controlled to examine multivariable associations. Fourth, the SEER-Medicare data are not developed for research purposes and therefore have limitations associated with its use for estimating healthcare expenditures. Fifth, the study included patients who were alive during the study period, which might have underestimated expenditures as patients receiving end-of-life care are anticipated to have higher expenditures and CAD-related hospitalizations. Further, those receiving end-of-life care are anticipated to have lower adherence. Lastly, prescription claims were used for measuring adherence. As part D file contains only filled prescriptions, it is not known whether the patient actually used the medications or whether the patients they adhered to their providers' instructions or not.

5.5 Suggestions for Future Research

The current study has implications for further investigation. Studies need to examine whether the proven strategies of medication adherence can also be applied to improve medication adherence of multiple drug regimens.

Our study findings indicated that those using single medication class and adherent to that single medication class were less likely to have CAD-related hospitalization compared to those who were adherent to both medication classes. In addition, the interaction between medication adherence categories and cardiotoxic cancer treatment on CAD-related hospitalization was not statistically significant. Therefore, future studies are needed to provide conclusive evidence on the role of CAD severity and unobserved factors (healthy eating, exercise, alternative and complementary medicine, and polypharmacy) for the stated findings.

Our study findings indicated that CAD-related expenditures were highest during the 120-day interval immediately following cancer diagnosis. This suggests that the period after cancer diagnosis is the crucial period for co-management of CAD and cancer. This is an interesting finding and needs further research to understand the cancer-related factors that might contribute to this increase in expenditures with time in those diagnosed with cancer.

Our study findings also indicated that those with colorectal cancer may be particularly at risk for high CAD-related healthcare expenditures. Future studies need to explore whether the emerging collaborative care models, such as medical homes, can reduce inpatient use, and consequently, CAD-related expenditures.

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Appendix A. Codes related to cancer diagnosis and treatment

Cancer/treatment	ICD-9-CM Codes Site recode ICD-O-3/WHO recodes	ICD-9-CM Procedure Codes	HCPSCS/CPT Codes	Revenue Center Codes
Cancer type				
Breast Cancer	26000	-	-	-
Colorectal Cancer	21041 - 21049, 21051 - 21052	-	-	-
Prostate Cancer	28010			
Cancer Treatment - Surgery				
Breast Cancer	-	8520-8529, 8533-8536, 8540-8548 4530-4534, 4541-4543, 4549, 4550- 4552, 4561-4563, 4570-4576, 4579, 4580-4583, 4590-4595, 4601, 4603, 4604, 4610, 4611, 4613, 4614, 4620-4623, 4835, 4840-4843, 4849- 4852, 4859-4865, 4869	19120, 19125, 9126, 19300-19307, 44140, 44141, 4143-44147, 4150, 44160, 44204-44208, 4150-44153, 44155, 4158, 44210-44212, 5160, 45170, 45171, 5110-45114, 45116, 5119-45121, 45123, 5126, 45395, 45397 55801, 55810, 5812, 55815, 5821, 55831, 55840, 55842, 5845, 55866	
Colorectal Cancer	-			
Prostate Cancer	-	602-606		
Cancer Treatment - Chemotherapy				
-	V581, V662, V672	9925, 9928	96401- 96549, Q0083-Q0085, J9000-J9999, S9329-S9331, J8501-8999, J0640	0331, 0332, 0335
Cancer Treatment - Radiation Therapy				
-	V580, V661, V671	9220-9239	77261-77799, C1715-C1720, C2634-C2699, C1728	0330, 0333

Abbreviations:

CPT-4: Common Procedural Terminology, 4th Edition; HCPSCS: Health Care Procedure Classification Code; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-O-3: International Classification of Diseases for Oncology, 3rd Edition; WHO: World Health Organization

Appendix B. List of statins

Monotherapy		Combination therapy	
Brand	Generic	Brand	Generic
Lipitor	Atorvastatin	Advicor	Lovastatin-Niacin
Lescol	Fluvastatin	Caudet	Atorvastatin-Amlodipine
Altocor, Mevacor	Lovastatin	Inegy	Simvastatin-Ezetimibe
Livalo	Pitavastatin	Simcor	Simvastatin-Niacin
Pravachol	Pravastatin	Juvisync	Simvastatin-Sitagliptin
Crestor	Rosuvastatin	Liptruzet	Ezetimibe/Atorvastatin calcium
Zocor	Simvastatin		

Appendix C. List of angiotensin-converting enzyme inhibitors

Monotherapy		Combination therapy	
Brand	Generic	Brand	Generic
Lotensin	Benazepril	Accuretic	Quinapril-Hydrochlorothiazide
Capoten	Captopril	Capozide	Captopril-Hydrochlorothiazide
Vasotec	Enalapril	Lexxel	Enalapril-Hydrochlorothiazide
Monopril	Fosinopril	Lotensin HCT	Benazepril-Hydrochlorothiazide
Prinivil, Zestril	Lisinopril	Lotrel	Benazepril-Amlodipine
Univasc	Moexipril	Monopril HCT	Fosinopril-Hydrochlorothiazide
Aceon	Perindopril	Prinizide, Zestoretic	Lisinopril-Hydrochlorothiazide
Accupril	Quinapril	Tarka	Trandolapril-Verapamil
Altace	Ramipril	Uniretic	Moexipril-Hydrochlorothiazide
Mavik	Trandolapril	Vasoteretic	Enalapril-Hydrochlorothiazide

Appendix D. List of angiotensin II receptor blockers

Monotherapy		Combination therapy	
Brand	Generic	Brand	Generic
Diovan	Valsartan	Atacand HCT	Candesartan-Hydrochlorothiazide
Atacand	Candesartan	Tevetan HCT	Eprosartan-Hydrochlorothiazide
Tevetan	Eprosartan	Avalide	Irbesartan-Hydrochlorothiazide
Avapro	Irbesartan	Hyzaar	Losartan-Hydrochlorothiazide
Cozaar	Losartan	Benicar HCT	Olmesartan-Hydrochlorothiazide
Benicar	Olmesartan	Micardis HCT	Telmisartan-Hydrochlorothiazide
Micardis	Telmisartan	Diovan HCT	Valsartan-Hydrochlorothiazide
Edarbi	Azilsartan	Azor	Olmesartan-Amlodipine
		Exforge	Valsartan-Amlodipine
		Exforge HCT	Valsartan-Amlodipine-Hydrochlorothiazide
		Valturna	Valsartan-Aliskerin
		Edarbyclor	Azilsartan-Chlorthalidone
		Tribenzor	Olmesartan-Amlodipine-Hydrochlorothiazide
		Twynsta	Telmisartan-Amlodipine

Appendix E. List of beta-blockers

Monotherapy		Combination therapy	
Brand	Generic	Brand	Generic
Betapace	Sotalol	Corzide	Nadolol-Bendroflumethiazide
Blocadren	Timolol	Inderide	Propanolol-Hydrochlorothiazide
Brevibloc	Esmolol	Tenoretic	Atenolol-Chlorthalidone
Cartrol	Carteolol	Ziac	Bisoprolol-Hydrochlorothiazide
Coreg	Carvedilol	Lopressor-HCT	Metoprolol-Hydrochlorothiazide
Corgard	Nadolol		
Inderal	Propanolol		
Kerlone	Betaxolol		
Levatol	Penbutolol		
Lopressor	Metoprolol		
Sectral	Acebutolol		
Tenormin	Atenolol		
Trandate Normodyne	Labetalol		
Visken	Pindolol		
Zebeta	Bisoprolol		
Bystolic	Nebivolol		

Appendix F. Heart disease ICD-9-CM diagnosis and procedure codes

Heart diseases	ICD-9-CM diagnosis/procedure code
Acute Myocardial infarction	410.01, 410.11, 410.21, 410.31, 410.41, 410.51, 410.61, 410.71, 410.81, 410.91
Ischemic Heart Disease	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 410.70, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92, 411.0, 411.1, 411.81, 411.89, 412, 413.0, 413.1, 413.9, 414.00, 414.01, 414.02, 414.03, 414.04, 414.05, 414.06, 414.07, 414.12, 414.2, 414.3, 414.4, 414.8, 414.9
Stroke / Transient Ischemic Attack	430, 431, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9, 436, 997.02
Heart Failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.0, 428.1, 428.20, 428.21, 428.22, 428.23, 428.30, 428.31, 428.32, 428.33, 428.40, 428.41, 428.42, 428.43, 428.9
CAD-related Procedures	0066, 3601, 3602, 3603, 3604, 3605, 3606, 3607, 3609, 3610, 3611, 3612, 3613, 3614, 3615, 3616, 3617, 3619, 362, 3631, 3632

Note: Other heart diseases (stroke and heart failure) and procedure codes were used for CAD-related hospitalization.